Today's hypertensives with new concerns...

The JNC now recommends selective alpha$_1$-blockers as a first choice[1]

THE CARDURA GENERATION

Choose CARDURA: first-line therapy for a new generation of hypertensives.

Choose CARDURA for around-the-clock blood pressure control that doesn't jeopardize blood lipids or blood sugar.[2-4]

CARDURA is well tolerated. In placebo-controlled studies, only three common side effects were reported significantly more often than with placebo: dizziness, somnolence, and fatigue. These were generally mild and transient. Only 2% of patients discontinued therapy due to adverse effects— the same as with placebo. Syncope has been reported, but rarely (<1%).

ONCE-A-DAY

CARDURA®

(doxazosin mesylate) Scored Tablets 1 mg, 2 mg, 4 mg, 8 mg

HYPERTENSION CONTROL FOR A NEW GENERATION.

Please see brief summary of prescribing information on next page.

ONCE-A-DAY

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(doxazosin mesylate) Scored Tablets 1 mg, 2 mg, 4 mg, 8 mg

References: 1. The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). *Arch Intern Med.* 1993;153:154-183. **2.** Pickering TG, the Hypertension and Lipid Trial Study Group. The use of 24-hour ambulatory monitoring in the assessment of antihypertensive therapy. Presented at the 1991 *American Academy of Family Physicians* 43rd Annual Assembly; September 24-29, 1991; Washington, DC. **3.** Neaton JD, Grimm RH Jr, Prineas RJ, et al for The Treatment of Mild Hypertension Research Group. Treatment of Mild Hypertension Study: final results. *JAMA.* 1993;270:713-724. **4.** Lehtonen A, the Finnish Multicenter Study Group. Lowered levels of serum insulin, glucose, and cholesterol in hypertensive patients during treatment with doxazosin. *Curr Ther Res.* 1990;47:278-284.

CARDURA® (doxazosin mesylate) Tablets
Brief Summary of Prescribing Information

INDICATIONS AND USAGE

CARDURA (doxazosin mesylate) is indicated for the treatment of hypertension. CARDURA may be used alone or in combination with diuretics or beta-adrenergic blocking agents. There is limited experience with CARDURA in combination with angiotensin converting enzyme inhibitors or calcium channel blockers.

CONTRAINDICATIONS

CARDURA is contraindicated in patients with a known sensitivity to quinazolines (e.g. prazosin, terazosin).

WARNINGS

Syncope and "First-dose" Effect:

Doxazosin, like other alpha-adrenergic blocking agents, can cause marked hypotension, especially in the upright position, with syncope and other postural symptoms such as dizziness. Marked orthostatic effects are most common with the first dose but can also occur when there is a dosage increase, or if therapy is interrupted for more than a few days. To decrease the likelihood of excessive hypotension and syncope, it is essential that treatment be initiated with the 1 mg dose. The 2, 4, and 8 mg tablets are not for initial therapy. Dosage should then be adjusted slowly (see DOSAGE AND ADMINISTRATION section) with increases in dose every two weeks. Additional antihypertensive agents should be added with caution.

Patients being titrated with doxazosin should be cautioned to avoid situations where injury could result should syncope occur.

In an early investigational study of the safety and tolerance of increasing daily doses of doxazosin in normotensives beginning at 1 mg/day, only 2 of 6 subjects could tolerate more than 2 mg/day without experiencing symptomatic postural hypotension. In another study of 24 healthy normotensive male subjects receiving initial doses of 2 mg/day of doxazosin, seven (29%) of the subjects experienced symptomatic postural hypotension between 0.5 and 6 hours after the first dose necessitating termination of the study. In this study 2 of the normotensive subjects experienced syncope. Subsequent trials in hypertensive patients always began doxazosin dosing at 1 mg/day resulting in a 4% incidence of postural side effects at 1 mg/day with no cases of syncope.

In multiple dose clinical trials involving over 1500 patients with dose titration every one to two weeks, syncope was reported in 0.7% of patients. None of these events occurred at the starting dose of 1 mg and 1.2% (8/664) occurred at 16 mg/day.

If syncope occurs, the patient should be placed in a recumbent position and treated supportively as necessary.

PRECAUTIONS

General

1. Orthostatic Hypotension:

While syncope is the most severe orthostatic effect of CARDURA, other symptoms of lowered blood pressure, such as dizziness, lightheadedness, or vertigo, can occur, especially at initiation of therapy or at the time of dose increases. These were common in clinical trials, occurring in up to 23% of all patients treated and causing discontinuation of therapy in about 2%.

In placebo controlled titration trials orthostatic effects were minimized by beginning therapy at 1 mg per day and titrating every two weeks to 2, 4, or 8 mg per day. There was an increased frequency of orthostatic effects in patients given 8 mg or more, 10%, compared to 5% at 1-4 mg and 3% in the placebo group.

Patients in occupations in which orthostatic hypotension could be dangerous should be treated with particular caution.

If hypotension occurs, the patient should be placed in the supine position and, if this measure is inadequate, volume expansion with intravenous fluids or vasopressor therapy may be used. A transient hypotensive response is not a contraindication to further doses of CARDURA.

2. Impaired liver function:

CARDURA should be administered with caution to patients with evidence of impaired hepatic function or to patients receiving drugs known to influence hepatic metabolism. There is no controlled clinical experience with CARDURA in patients with these conditions.

3. Leukopenia/Neutropenia:

Analysis of hematologic data from patients receiving CARDURA in controlled clinical trials showed that the mean WBC (N=474) and mean neutrophil counts (N=419) were decreased by 2.4% and 1.0% respectively, compared to placebo, a phenomenon seen with other alpha blocking drugs. A search through a data base of 2400 patients revealed 4 in which drug-related neutropenia could not be ruled out. Two had a single low value on the last day of treatment. Two had stable, non-progressive neutrophil counts in the 1000/mm³ range over periods of 20 and 40 weeks. In cases where follow-up was available the WBCs and neutrophil counts returned to normal after discontinuation of CARDURA. No patients became symptomatic as a result of the low WBC or neutrophil counts.

Information for Patients:

Patients should be made aware of the possibility of syncopal and orthostatic symptoms, especially at the initiation of therapy, and urged to avoid driving or hazardous tasks for 24 hours after the first dose, after a dosage increase, and after interruption of therapy when treatment is resumed. They should be cautioned to avoid situations where injury could result should syncope occur during initiation of doxazosin therapy. They should also be advised of the need to sit or lie down when symptoms of lowered blood pressure occur, although these symptoms are not always orthostatic, and to be careful when rising from a sitting or lying position. If dizziness, lightheadedness, or palpitations are bothersome they should be reported to the physician, so that dose adjustment can be considered. Patients should also be told that drowsiness or somnolence can occur with doxazosin, requiring caution in people who must drive or operate heavy machinery.

Drug Interactions:

Most (98%) of plasma doxazosin is protein bound. *In vitro* data in human plasma indicate that CARDURA has no effect on protein binding of digoxin, warfarin, phenytoin or indomethacin. There is no information on the effect of other highly plasma protein bound drugs on doxazosin binding. CARDURA has been administered without any evidence of an adverse drug interaction to patients receiving thiazide diuretics, beta blocking agents, and nonsteroidal anti-inflammatory drugs.

Cimetidine:

In a placebo-controlled trial in normal volunteers, the administration of a single 1 mg dose of doxazosin on day 1 of a four-day regimen of oral cimetidine (400 mg twice daily) resulted in a 10% increase in mean AUC of doxazosin (p=0.006), and a slight but not statistically significant increase in mean C_{max} and mean half-life of doxazosin. The clinical significance of this increase in doxazosin AUC is unknown.

Drug/Laboratory test interactions:

None known.

Cardiac Toxicity in Animals:

An increased incidence of myocardial necrosis or fibrosis was displayed by Sprague-Dawley rats after 6 months of dietary administration at concentrations calculated to provide 80 mg doxazosin/kg/day and after 12 months of dietary administration at concentrations calculated to provide 40 mg doxazosin/kg/day (150 times the maximum recommended human dose assuming a patient weight of 60 kg). Myocardial fibrosis was observed in both rats and mice treated in the same manner with 40 mg doxazosin/kg/day for 18 months. No cardiotoxicity was observed at lower doses (up to 10 or 20 mg/kg/day, depending on the study) in either species. These lesions were not observed after 12 months of oral dosing in dogs and Wistar rats at maximum doses of 20 mg/kg/day and 100 mg/kg/day, respectively. There is no evidence that similar lesions occur in humans.

Carcinogenesis, Mutagenesis and Impairment of Fertility:

Chronic dietary administration (up to 24 months) of doxazosin mesylate at maximally tolerated concentrations (highest dose 40 mg/kg: about 150 times the maximum recommended human dose of 16 mg/60 kg) revealed no evidence of carcinogenicity in rats. There was also no evidence of carcinogenicity in a similarly conducted study (up to 18 months of dietary administration) in mice. The mouse study, however, was compromised by the failure to use a maximally tolerated dose of doxazosin.

Mutagenicity studies revealed no drug- or metabolite-related effects at either chromosomal or subchromosomal levels.

Studies in rats showed reduced fertility in males treated with doxazosin at oral doses of 20 (but not 5 or 10) mg/kg/day, about 75 times the maximum recommended human dose. This effect was reversible within two weeks of drug withdrawal.

Pregnancy

Teratogenic Effects, Pregnancy Category C. Studies in pregnant rabbits and rats at daily oral doses of up to 41 and 20 mg/kg, respectively (154 and 75 times the maximum recommended daily dose of 16 mg, assuming a patient weight of 60 kg), have revealed no evidence of harm to the fetus. A dosage regimen of 82 mg/kg/day in the rabbit was associated with reduced fetal survival. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, CARDURA should be used during pregnancy only if clearly needed.

Radioactivity was found to cross the placenta following oral administration of labelled doxazosin to pregnant rats.

Nonteratogenic Effects. In peri-postnatal studies in rats, postnatal development at maternal doses of 40 or 50 mg/kg/day of doxazosin was delayed as evidenced by slower body weight gain and a slightly later appearance of anatomical features and reflexes.

Nursing Mothers

Studies in lactating rats given a single oral dose of 1 mg/kg of [2-^{14}C]-doxazosin indicate that doxazosin accumulates in rat breast milk with a maximum concentration about 20 times greater than the maternal plasma concentration. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when CARDURA is administered to a nursing mother.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

CARDURA has been administered to approximately 4000 patients, of whom 1679 were included in the clinical development program. In that program, minor adverse effects were frequent, but led to discontinuation of treatment in only 7% of patients. In placebo-controlled studies adverse effects occurred in 49% and 40% of patients in the doxazosin and placebo groups, respectively, and led to discontinuation in 2% of patients in each group. The major reasons for discontinuation were postural effects (2%), edema, malaise/fatigue, and some heart rate disturbance, each about 0.7%.

In controlled clinical trials directly comparing CARDURA to placebo there was no significant difference in the incidence of side effects, except for dizziness (including postural), weight gain, somnolence and fatigue/malaise. Postural effects and edema appeared to be dose related.

The prevalence rates presented below are based on combined data from placebo-controlled studies involving once daily administration of doxazosin at doses ranging from 1-16 mg. The following summarizes those adverse experiences (possibly/probably related) reported for patients in these studies where the prevalence rate in the doxazosin group was at least 0.5% or where the reaction is of particular interest.

Adverse reactions during placebo-controlled studies with doxazosin (n=339) and placebo (n=336), respectively:

Cardiovascular—*Dizziness:* 19% and 9%; *Vertigo:* 2% and 1%; *Postural Hypotension:* 0.3% and 0%; *Edema:* 4% and 3%; *Palpitation:* 2% and 3%; *Arrhythmia:* 1% and 0%; *Hypotension:* 1% and 0%; *Tachycardia:* 0.3% and 1%; *Peripheral Ischemia:* 0.3% and 0%; **Skin Appendages**—*Rash:* 1% and 1%; *Pruritus:* 1% and 1%; **Musculoskeletal**—*Arthralgia/Arthritis:* 1% and 0%; *Muscle Weakness:* 1% and 0%; *Myalgia:* 1% and 0%; **Central & Peripheral N.S.**—*Headache:* 14% and 16%; *Paresthesia:* 1% and 1%; *Kinetic Disorders:* 1% and 0%; *Ataxia:* 1% and 0%; *Hypertonia:* 1% and 0%; *Muscle Cramps:* 1% and 0%; **Autonomic**—*Mouth Dry:* 2% and 2%; *Flushing:* 1% and 0%; **Special Senses**—*Vision Abnormal:* 2% and 1%; *Conjunctivitis/Eye Pain:* 1% and 1%; *Tinnitus:* 1% and 0.3%; **Psychiatric**—*Somnolence:* 5% and 1%; *Nervousness:* 2% and 2%; *Depression:* 1% and 1%; *Insomnia:* 1% and 1%; *Sexual Dysfunction:* 2% and 1%; **Gastrointestinal**—*Nausea:* 3% and 4%; *Diarrhea:* 2% and 3%; *Constipation:* 1% and 1%; *Dyspepsia:* 1% and 1%; *Flatulence:* 1% and 1%; *Abdominal Pain:* 0% and 2%; *Vomiting:* 0% and 1%; **Respiratory**—*Rhinitis:* 3% and 1%; *Dyspnea:* 1% and 1%; *Epistaxis:* 1% and 0%; **Urinary**—*Polyuria:* 2% and 0%; *Urinary Incontinence:* 1% and 0%; *Micturation Frequency:* 0% and 2%; **General**—*Fatigue/Malaise:* 12% and 6%; *Chest Pain:* 2% and 2%; *Asthenia:* 1% and 1%; *Face Edema:* 1% and 0%; *Pain:* 2% and 2%.

Additional adverse reactions have been reported, but these are, in general, not distinguishable from symptoms that might have occurred in the absence of exposure to doxazosin. The following adverse reactions occurred with a frequency of between 0.5% and 1%: syncope, hypoesthesia, increased sweating, agitation, increased weight. The following additional adverse reactions were reported by <0.5% of 3960 patients who received doxazosin in controlled or open, short- or long-term clinical studies, including international studies. *Cardiovascular System:* angina pectoris, myocardial infarction, cerebrovascular accident; *Autonomic Nervous System:* pallor; *Metabolic:* thirst, gout, hypokalemia; *Hematopoietic:* lymphadenopathy, purpura; *Reproductive System:* breast pain; *Skin Disorders:* alopecia, dry skin, eczema; *Central Nervous System:* paresis, tremor, twitching, confusion, migraine, impaired concentration; *Psychiatric:* paroniria, amnesia, emotional lability, abnormal thinking, depersonalization; *Special Senses:* parosmia, earache, taste perversion, photophobia, abnormal lacrimation; *Gastrointestinal System:* increased appetite, anorexia, fecal incontinence, gastroenteritis; *Respiratory System:* bronchospasm, sinusitis, coughing, pharyngitis; *Urinary System:* renal calculus; *General Body System:* hot flushes, back pain, infection, fever/rigors, decreased weight, influenza-like symptoms.

CARDURA has not been associated with any clinically significant changes in routine biochemical tests. No clinically relevant adverse effects were noted on serum potassium, serum glucose, uric acid, blood urea nitrogen, creatinine or liver function tests. CARDURA has been associated with decreases in white blood cell counts (See Precautions).

OVERDOSAGE

No data are available in regard to overdosage in humans.

The oral LD_{50} of doxazosin is greater than 1000 mg/kg in mice and rats. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of fluid. As doxazosin is highly protein bound, dialysis would not be indicated.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED. The initial dosage of CARDURA in hypertensive patients is 1 mg given once daily. This starting dose is intended to minimize the frequency of postural hypotension and first dose syncope associated with CARDURA. Postural effects are most likely to occur between 2 and 6 hours after a dose. Therefore blood pressure measurements should be taken during this time period after the first dose and with each increase in dose. Depending on the individual patient's standing blood pressure response (based on measurements taken at 2-6 hours postdose and 24 hours postdose), dosage may then be increased to 2 mg and thereafter if necessary to 4 mg, 8 mg and 16 mg to achieve the desired reduction in blood pressure. **Increases in dose beyond 4 mg increase the likelihood of excessive postural effects including syncope, postural dizziness/vertigo, postural hypotension. At a titrated dose of 16 mg once daily the frequency of postural effects is about 12% compared to 3% for placebo.**

More detailed professional information available on request.

65-4538-00-1 Revised January 1993

Pfizer Roerig

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- First and only nonacidic NSAID†
- As effective as NSAID standards for OA and RA[1]
- 0.5% cumulative incidence of peptic ulcer up to 1 year[1]
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* GI symptoms comparable to other NSAIDs, including diarrhea, dyspepsia, and abdominal pain. In patients treated chronically with NSAID therapy, serious GI toxicity such as perforation, ulceration, and bleeding can occur.

† *Relafen* is biotransformed in the liver to the active metabolite 6-methoxy-2-naphthylacetic acid.

Contraindicated in patients who are hypersensitive to aspirin or other NSAIDs.

As with other NSAIDs, rare renal and hepatic reactions have been reported. Please see precautions section of prescribing information.

Please see brief summary of prescribing information on adjacent page.

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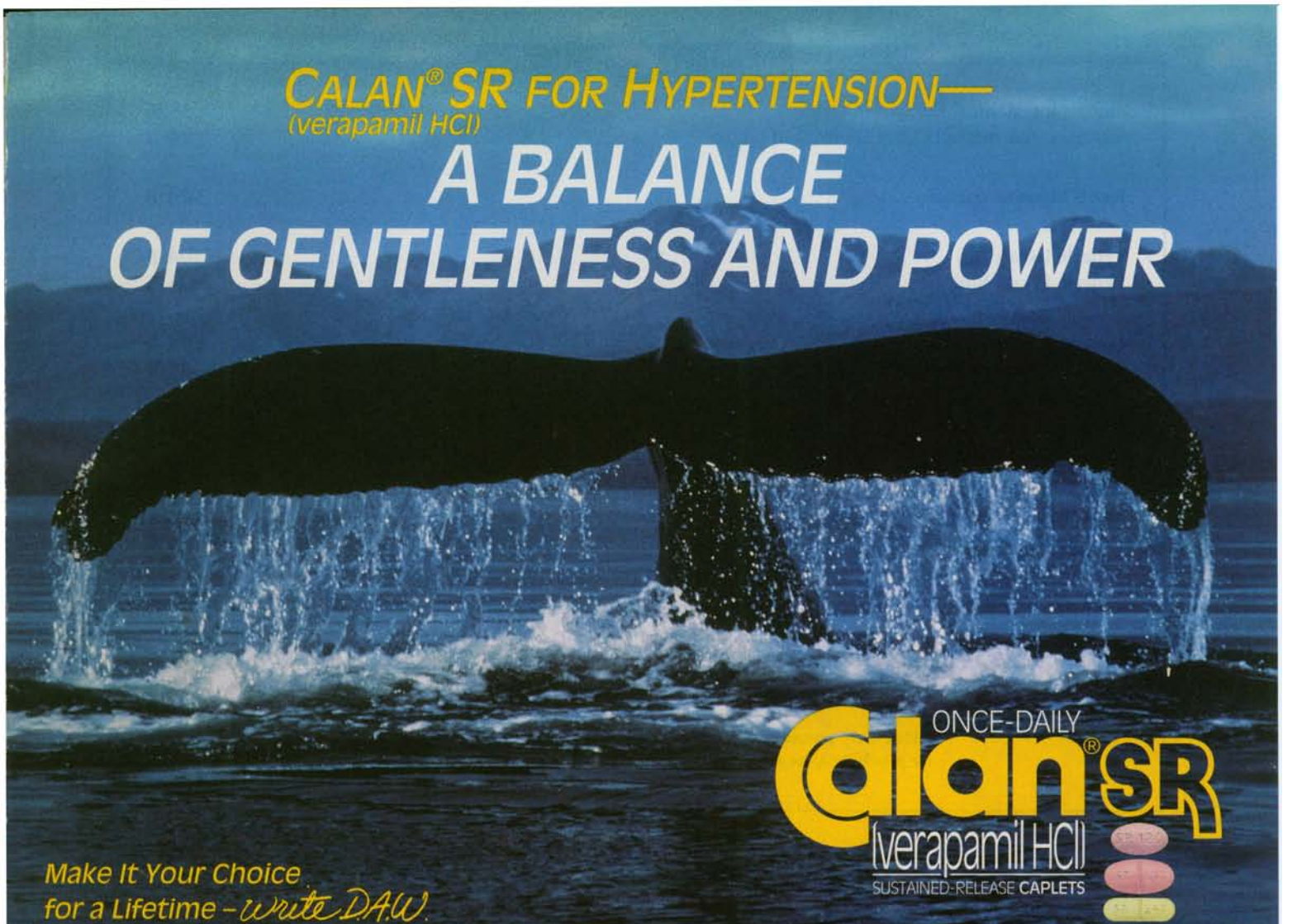

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The recommended starting dosage for Calan SR is 180 mg once daily. Dose titration will be required in some patients to achieve blood pressure control. A lower starting dosage of 120 mg/day may be warranted in some patients (eg, the elderly, patients of small stature). Dosages above 240 mg daily should be administered in divided doses. Calan SR should be administered with food. Constipation, which is easily managed in most patients, is the most commonly reported side effect of Calan SR.

BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol and propranolol clearance may occur when either drug is administered concomitantly with verapamil. A variable effect has been seen with combined use of atenolol. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hyperrtrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in an increased sensitivity to lithium (neurotoxicity), with either no change or an increase in serum lithium levels; however, it may also result in a lowering of serum lithium levels. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and increase the plasma levels of theophylline. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. There was no evidence of a carcinogenic potential of verapamil administered to rats for 2 years. A study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes, reversible non-obstructive paralytic ileus. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

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Reference: 1. Cady RK, Wendt JK, Kirchner JR, Sargent JD, Rothrock JF, Skaggs H Jr. Treatment of acute migraine with subcutaneous sumatriptan. *JAMA*. June 1991;265:2831-2835.

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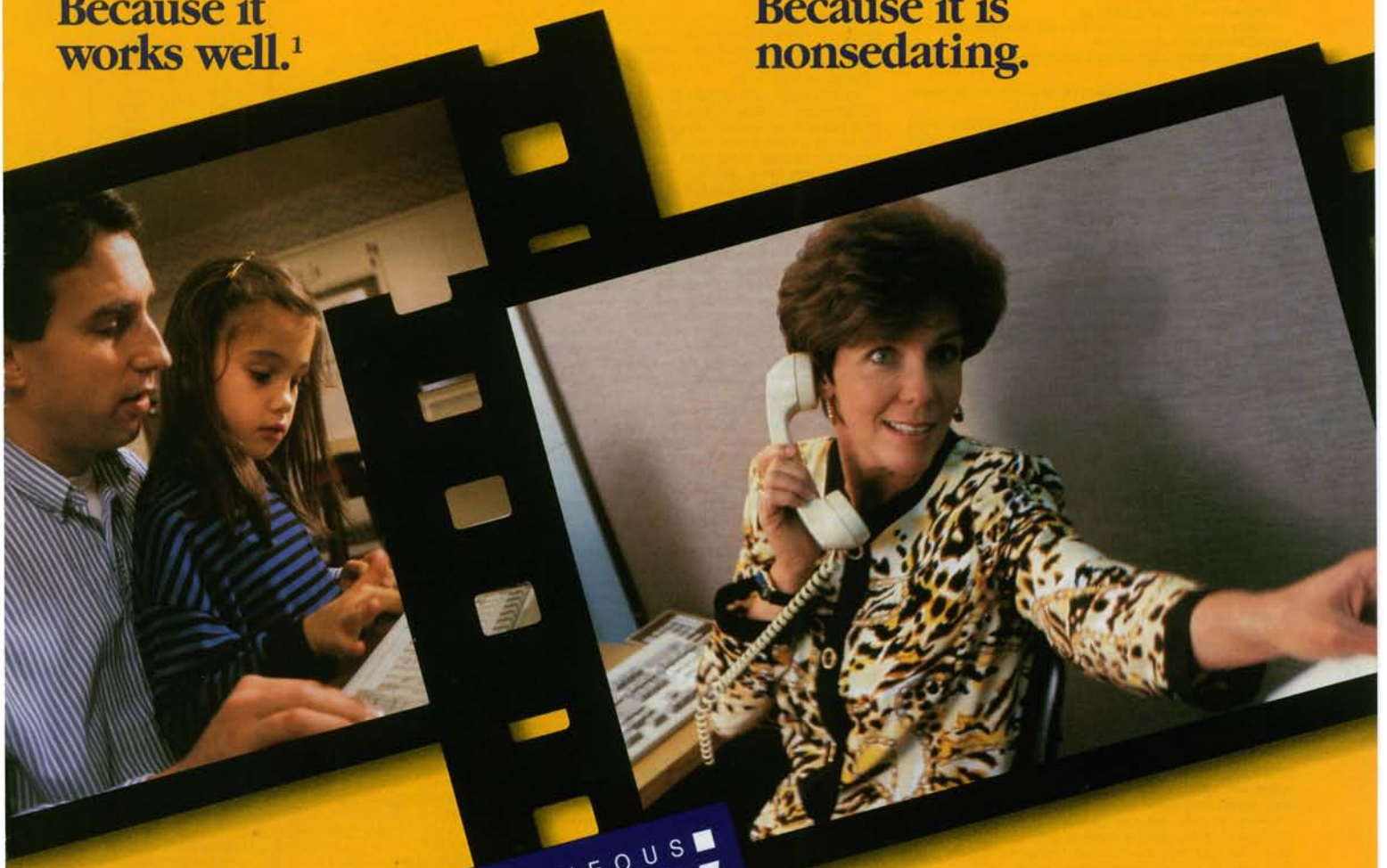
Because it works well.[1]

Because it is nonsedating.



SUBCUTANEOUS

IMITREX®

SUMATRIPTAN SUCCINATE

MIGRAINE RELIEF THAT CAN CHANGE PATIENTS' LIVES

Please consult Brief Summary of Prescribing Information on last page of this advertisement.

BRIEF SUMMARY

Imitrex® (sumatriptan succinate) Injection

For Subcutaneous Use Only.

The following is a brief summary only. Before prescribing, see complete prescribing information in Imitrex® Injection product labeling.

INDICATIONS AND USAGE: Imitrex® Injection is indicated for the acute treatment of migraine attacks with or without aura.

Imitrex Injection is not for use in the management of hemiplegic or basilar migraine (see WARNINGS).

Safety and effectiveness have also not been established for cluster headache, which is present in an older, predominantly male population.

CONTRAINDICATIONS: Imitrex® Injection should not be given intravenously because of its potential to cause coronary vasospasm.

For similar reasons, Imitrex Injection should not be given subcutaneously to patients with ischemic heart disease (angina pectoris, history of myocardial infarction, or documented silent ischemia) or to patients with Prinzmetal's angina. Also, patients with symptoms or signs consistent with ischemic heart disease should not receive Imitrex Injection. Because Imitrex Injection can give rise to increases in blood pressure (usually small), it should not be given to patients with uncontrolled hypertension.

Imitrex Injection should not be used concomitantly with ergotamine-containing preparations.

Imitrex Injection is contraindicated in patients with hypersensitivity to sumatriptan.

WARNINGS: Imitrex® Injection should not be administered to patients with basilar or hemiplegic migraine.

Cardiac Events/Coronary Constriction: Serious coronary events following Imitrex Injection can occur but are extremely rare; nonetheless, **consideration should be given to administering the first dose of Imitrex Injection in the physician's office to patients in whom unrecognized coronary disease is comparatively likely** (postmenopausal women; males over 40; patients with risk factors for CAD, such as hypertension, hypercholesterolemia, obesity, diabetes, smokers, and strong family history). **If symptoms consistent with angina occur, electrocardiographic (ECG) evaluation should be carried out to look for ischemic changes.**

Sumatriptan may cause coronary vasospasm in patients with a history of coronary artery disease, who are known to be more susceptible than others to coronary artery vasospasm, and, rarely, in patients without prior history suggestive of coronary artery disease. There were eight patients among the more than 1,900 who participated in controlled trials who sustained clinical events during or shortly after receiving subcutaneous sumatriptan that may have reflected coronary vasospasm. Six of these eight patients had ECG changes consistent with transient ischemia, but without symptoms or signs. Of the eight patients, four had some findings suggestive of coronary artery disease prior to treatment. None of these adverse events was associated with a serious clinical outcome.

There have been rare reports from countries in which Imitrex Injection has been marketed of serious and/or life-threatening arrhythmias, including atrial fibrillation, ventricular fibrillation, ventricular tachycardia; myocardial infarction; and marked ischemic ST elevations associated with Imitrex Injection. In addition, there have been rare, but more frequent, reports of chest and arm discomfort thought to represent angina pectoris.

Use in Women of Childbearing Potential: (see PRECAUTIONS)

PRECAUTIONS:

General: Chest, jaw, or neck tightness is relatively common after Imitrex® Injection, but has only rarely been associated with ischemic ECG changes.

Imitrex Injection may cause mild, transient elevation of blood pressure and peripheral vascular resistance.

Imitrex Injection should also be administered with caution to patients with diseases that may alter the absorption, metabolism, or excretion of drugs, such as impaired hepatic or renal function.

As with other acute migraine therapies, before treating headaches in patients not previously diagnosed as migraineurs and in migraineurs who present with atypical symptoms, care should be taken to exclude other potentially serious neurological conditions. There have been rare reports where patients received sumatriptan for severe headaches that were subsequently shown to have been secondary to an evolving neurological lesion (cerebrovascular accident, subarachnoid hemorrhage). In this regard, it should be noted that migraineurs may be at increased risk of certain cerebrovascular events (e.g., cerebrovascular accident, transient ischemic attack).

Although written instructions are supplied with the autoinjector, patients who are advised to self-administer Imitrex Injection in medically unsupervised situations should receive instruction on the proper use of the product from the physician or other suitably qualified health care professional prior to doing so for the first time.

Information for Patients: See PATIENT INFORMATION at the end of the product package insert for the text of the separate leaflet provided for patients.

Laboratory Tests: No specific laboratory tests are recommended for monitoring patients prior to and/or after treatment with Imitrex Injection.

Drug Interactions: There is no evidence that concomitant use of migraine prophylactic medications has any effect on the efficacy or unwanted effects of sumatriptan. In two Phase III trials in the US, a retrospective analysis of 282 patients who had been using prophylactic drugs (verapamil n=63, amitriptyline n=57, propranolol n=94, for 45 other drugs n=123) were compared to those who had not used prophylaxis (n=452). There were no differences in relief rates at 60 minutes postdose for Imitrex Injection, whether or not prophylactic medications were used. There were also no differences in overall adverse event rates between the two groups.

Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use of ergotamine and sumatriptan within 24 hours of each other should be avoided (see CONTRAINDICATIONS).

Drug/Laboratory Test Interactions: Imitrex Injection is not known to interfere with commonly employed clinical laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 104-week lifetime study in rats given sumatriptan by oral gavage, serum concentrations achieved were dose related, ranging at the low dose from approximately twice the peak concentration of the drug after the recommended human subcutaneous dose of 6 mg to more than 100 times this concentration at the high dose. There was no evidence of an increase in tumors considered to be related to sumatriptan administration.

In a 78-week study in which mice received sumatriptan continuously in drinking water, there was no evidence for an increase in tumors considered to be related to sumatriptan administration. That study, however, did not use the maximum tolerated dose and therefore did not fully explore the carcinogenic potential of Imitrex® (sumatriptan succinate) Injection in the mouse.

A Segment I rat fertility study by the subcutaneous route has shown no evidence of impaired fertility.

Pregnancy: ***Pregnancy Category C:*** Sumatriptan has been shown to be embryolethal in rabbits when given in daily doses producing plasma levels 3-fold higher than those attained following a 6-mg subcutaneous injection (i.e., recommended dose) to humans. There is no evidence that establishes that sumatriptan is a human teratogen; however, there are no adequate and well-controlled studies in pregnant women. Imitrex Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In assessing this information, the following additional findings should be considered.

Embryolethality: When given intravenously to pregnant rabbits daily throughout the period of organogenesis, sumatriptan caused embryolethality at doses at or close to those producing maternal toxicity. The mechanism of the embryolethality is not known. At these doses, peak concentrations of drug in plasma were more than 3-fold higher than the range observed in humans after the recommended subcutaneous dose of 6 mg.

The intravenous administration of sumatriptan to pregnant rats throughout organogenesis at doses producing plasma concentrations more than 50 times those seen after the recommended subcutaneous human dose did not cause embryolethality. In a study of pregnant rats given subcutaneous sumatriptan daily prior to and throughout pregnancy, there was no evidence of increased embryo/fetal lethality.

Teratogenicity: Term fetuses from Dutch Stride rabbits treated during organogenesis with oral sumatriptan exhibited an increased incidence of cervicothoracic vascular defects and minor skeletal abnormalities. The functional significance of these abnormalities is not known.

In a study in rats dosed daily with subcutaneous sumatriptan prior to and throughout pregnancy, there was no evidence of teratogenicity.

Studies in rats and rabbits evaluating the teratogenic potential of sumatriptan administered subcutaneously only during organogenesis (standard Segment II studies) have not been performed.

Nursing Mothers: Sumatriptan is excreted in breast milk in animals. No data exist in humans. Therefore, caution should be exercised when considering the administration of Imitrex Injection to a nursing woman.

Pediatric Use: Safety and effectiveness of Imitrex Injection in children have not been established.

Use in the Elderly: The safety and effectiveness of Imitrex Injection in individuals over age 65 have not been systematically evaluated. However, the pharmacokinetic disposition of Imitrex Injection in the elderly is similar to that seen in younger adults. No unusual adverse, age-related phenomena have been identified in patients over the age of 60 who participated in clinical trials with Imitrex Injection.

ADVERSE REACTIONS: (see also PRECAUTIONS) Sumatriptan may cause coronary vasospasm in patients with a history of coronary artery disease, known to be susceptible to coronary artery vasospasm, and, very rarely, without prior history suggestive of coronary artery disease.

There have been rare reports from countries in which Imitrex® Injection has been marketed of serious and/or life-threatening arrhythmias, including atrial fibrillation, ventricular fibrillation, ventricular tachycardia; myocardial infarction; and marked ischemic ST elevations associated with Imitrex Injection (see WARNINGS). More often, there has been chest discomfort that appeared to represent angina pectoris.

Other untoward clinical events associated with the use of subcutaneous Imitrex Injection are: pain or redness at the injection site, atypical sensations (such as sensations of warmth, cold, tingling or paresthesia, pressure, burning, numbness, tightness, all of which may be localized or generalized), flushing, chest symptoms (pressure, pain, or tightness), fatigue, dizziness, and drowsiness. All these untoward effects are usually transient, although they may be severe in some patients. Transient rises in blood pressure soon after treatment have been recorded.

Among patients in clinical trials of subcutaneous Imitrex Injection (n=6,218), up to 3.5% of patients withdrew for reasons related to adverse events.

Incidence in Controlled Clinical Trials: The following Table lists adverse events that occurred in two large US, Phase III, placebo-controlled clinical trials following either a single dose of Imitrex Injection or placebo. Only events that occurred at a frequency of 1% or more in Imitrex Injection treatment groups and were at least as frequent as in the placebo group are included in Table.

Treatment-Emergent Adverse Experience Incidence in Two Large Placebo-Controlled Clinical Trials: Events Reported by at Least 1% of Imitrex Injection Patients

	Percent of Patients Reporting	
Adverse Event Type	Imitrex Injection 6 mg SC n=547	Placebo n=370
Atypical sensations	42.0	9.2
Tingling	13.5	3.0
Warm/hot sensation	10.8	3.5
Burning sensation	7.5	0.3
Feeling of heaviness	7.3	1.1
Pressure sensation	7.1	1.6
Feeling of tightness	5.1	0.3
Numbness	4.6	2.2
Feeling strange	2.2	0.3
Tight feeling in head	2.2	0.3
Cold sensation	1.1	0.5
Cardiovascular		
Flushing	6.6	2.4
Chest discomfort	4.5	1.4
Tightness in chest	2.7	0.5
Pressure in chest	1.8	0.3
Ear, nose, and throat		
Throat discomfort	3.3	0.5
Discomfort: nasal cavity/sinuses	2.2	0.3
Eye		
Vision alterations	1.1	0.0
Gastrointestinal		
Abdominal discomfort	1.3	0.8
Dysphagia	1.1	0.0
Injection site reaction	58.7	23.8
Miscellaneous		
Jaw discomfort	1.8	0.0
Mouth and teeth		
Discomfort of mouth/tongue	4.9	4.6
Musculoskeletal		
Weakness	4.9	0.3
Neck pain/stiffness	4.8	0.5
Myalgia	1.8	0.5
Muscle cramp(s)	1.1	0.0
Neurological		
Dizziness/vertigo	11.9	4.3
Drowsiness/sedation	2.7	2.2
Headache	2.2	0.3
Anxiety	1.1	0.5
Malaise/fatigue	1.1	0.8
Skin		
Sweating	1.6	1.1

The sum of the percentages cited are greater than 100% because patients may experience more than one type of adverse event. Only events that occurred at a frequency of 1% or more in Imitrex® (sumatriptan succinate) Injection treatment groups and were at least as frequent as in the placebo groups are included.

Other Events Observed in Association With the Administration of Imitrex Injection: In the paragraphs that follow, the frequency of less commonly reported adverse clinical events are presented. Because the reports cite events observed in open and uncontrolled studies, the role of Imitrex Injection in their causation cannot be reliably determined. Furthermore, variability associated with reporting requirements, the terminology used to describe adverse events, etc., limit the value of the quantitative frequency estimates provided.

Event frequencies are calculated as the number of patients reporting an event divided by the total number of patients (n=6,218) exposed to subcutaneous Imitrex Injection. Given their imprecision, frequencies for specific adverse event occurrences are defined as follows: "infrequent" indicates a frequency estimated as falling between 1/1,000 and 1/100; "rare," a frequency less than 1/1,000.

Cardiovascular: Infrequent were hypertension, hypotension, bradycardia, tachycardia, palpitations, pulsating sensations, various transient ECG changes (nonspecific ST or T wave changes, prolongation of PR or QTc intervals, sinus arrhythmia, nonsustained ventricular premature beats, isolated junctional ectopic beats, atrial ectopic beats, delayed activation of the right ventricle), and syncope. Rare were pallor, arrhythmia, abnormal pulse, vasodilatation, and Raynaud's syndrome.

Endocrine and Metabolic: Infrequent was thirst. Rare were polydipsia and dehydration.

Eye: Infrequent was irritation of the eye.

Gastrointestinal: Infrequent were gastroesophageal reflux, diarrhea, and disturbances of liver function tests. Rare were peptic ulcer, retching, flatulence/eructation, and gallstones.

Musculoskeletal: Infrequent were various joint disturbances (pain, stiffness, swelling, ache). Rare were muscle stiffness, need to flex calf muscles, backache, muscle tiredness, and swelling of the extremities.

Neurological: Infrequent were mental confusion, euphoria, agitation, relaxation, chills, sensation of lightness, tremor, shivering, disturbances of taste, prickling sensations, paresthesia, stinging sensations, headaches, facial pain, photophobia, and lachrymation. Rare were transient hemiplegia, hysteria, globus hystericus, intoxication, depression, myoclonia, monoplegia/diplegia, sleep disturbance, difficulties in concentration, disturbances of smell, hyperesthesia, dysesthesia, simultaneous hot and cold sensations, tickling sensations, dysarthria, yawning, reduced appetite, hunger, and dystonia.

Respiratory: Infrequent was dyspnea. Rare were influenza, diseases of the lower respiratory tract, and hiccoughs.

Dermatological: Infrequent were erythema, pruritus, and skin rashes and eruptions. Rare was skin tenderness.

Urogenital: Rare were dysuria, frequency, dysmenorrhea, and renal calculus.

Miscellaneous: Infrequent were miscellaneous laboratory abnormalities, including minor disturbances in liver function tests, "serotonin agonist effect," and hypersensitivity to various agents. Rare was fever.

Postmarketing Experience: Frequency and causality for sumatriptan are not established for many of the following reports, which come from worldwide postmarketing experience: Episodes of Prinzmetal's angina, myocardial infarction, acute renal failure, seizure, cerebrovascular accident, dysphasia, subarachnoid hemorrhage, and arrhythmias (atrial fibrillation, ventricular fibrillation, and ventricular tachycardia). Hypersensitivity to Imitrex Injection has been reported, including anaphylactoid reactions, rash, urticaria, pruritus, erythema, and shortness of breath.

DRUG ABUSE AND DEPENDENCE: The abuse potential of Imitrex® Injection cannot be fully delineated in advance of extensive marketing experience. One clinical study enrolling 12 patients with a history of substance abuse failed to induce subjective behavior and/or physiologic response ordinarily associated with drugs that have an established potential for abuse.

CERENEX™ PHARMACEUTICALS
DIVISION OF GLAXO INC
Research Triangle Park, NC 27709

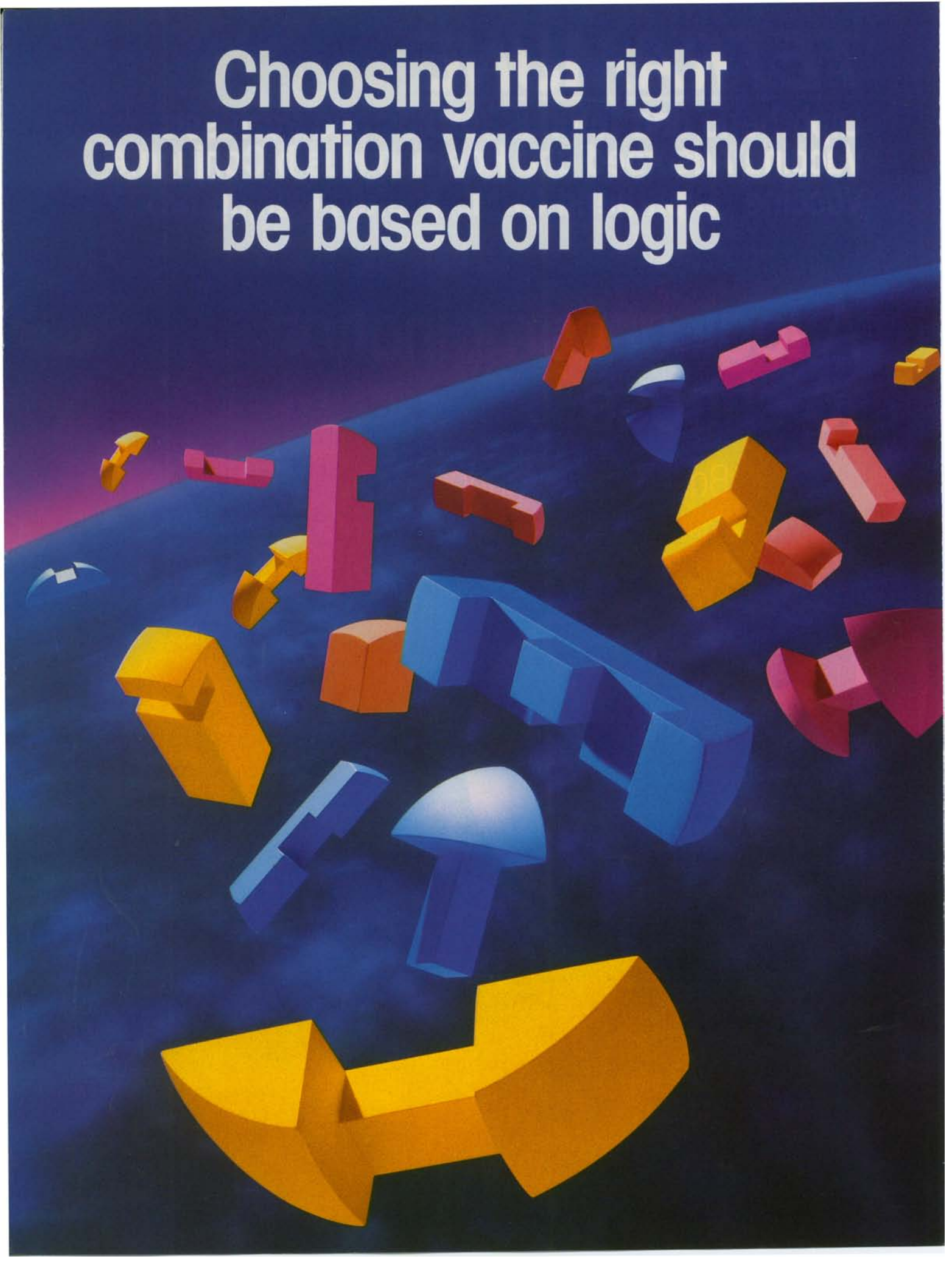
October 1993 RL-070 SUC8

IMX455RO

Printed in USA

January 1994

Choosing the right combination vaccine should be based on logic



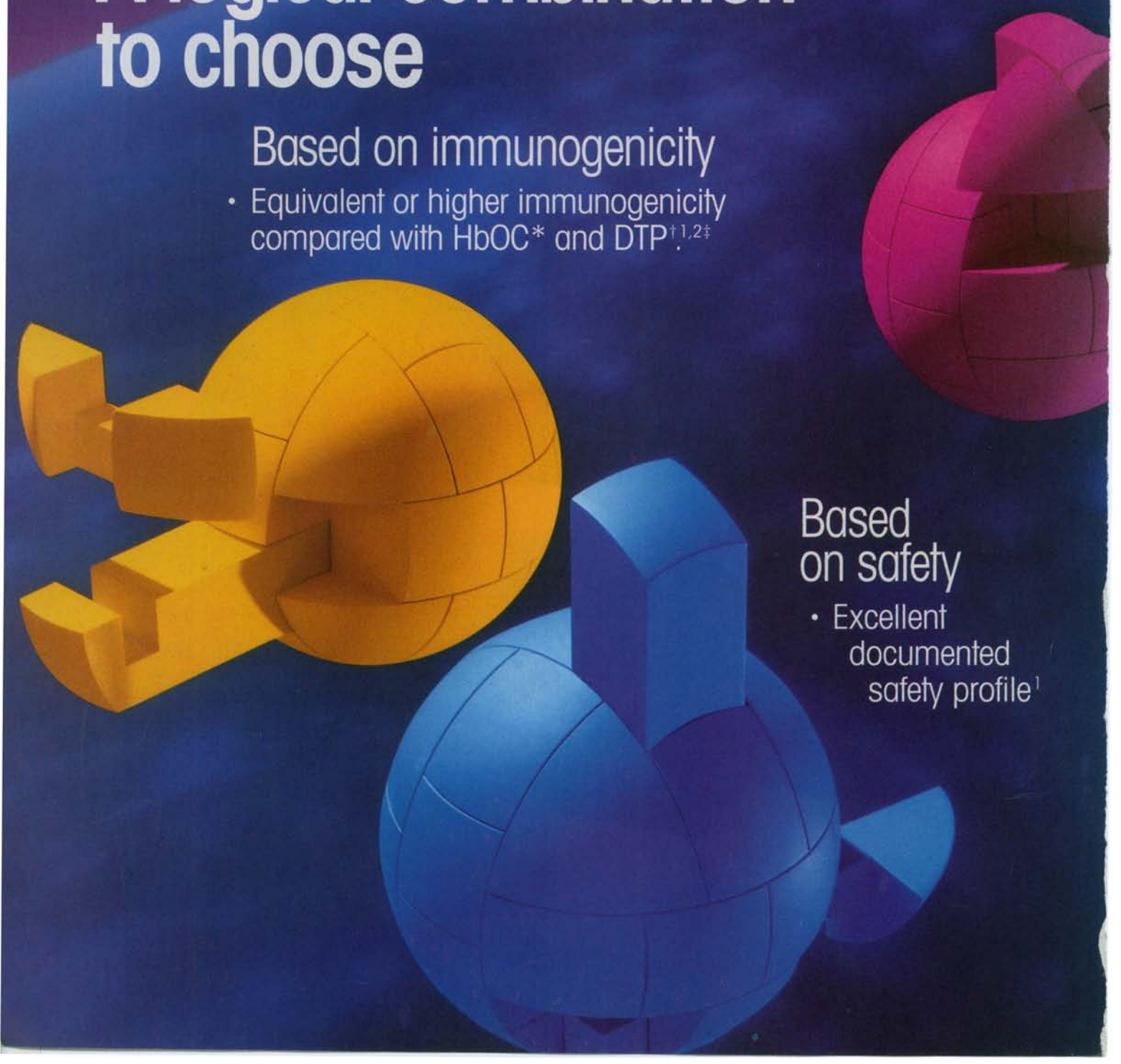
TETRAMUNE™

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed and Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate)

A logical combination to choose

Based on immunogenicity

- Equivalent or higher immunogenicity compared with HbOC* and DTP†.[1,2‡]



Based on safety

- Excellent documented safety profile[1]

Based on convenience

- Ready-to-use, 10-dose vials — *no reconstitution required*

Based on recommended scheduling

- Recommended by the AAP and the ACIP
- A single 0.5 mL injection recommended at 2, 4, 6, and 15 months of age§

*Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate). Manufactured by Praxis Biologics, Inc.

†Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed. Manufactured by Lederle Laboratories.

‡Higher antibody titers cannot be directly translated to mean higher efficacy.

§DTaP or DTP should be given at 4 to 6 years of age to complete the recommended 5-dose DTP immunization series.

References: 1. Data on file. Lederle Laboratories and Praxis Biologics, Inc., NY. **2.** Parodiso P, Hogerman D, Madore D, et al. Safety and immunogenicity in infants of a tetravalent vaccine composed of HbOC (HibTITER®) and DTP (TRI-IMMUNOL®). *Pediatr Res.* 1992;31(4). Abstract #1028.

To order, call 1-800-L-E-D-E-R-L-E (533-3753) or contact your local Lederle Medical Representative.

TETRAMUNE™

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed and Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate)

Please consult brief summary of full Prescribing Information on adjacent page.

Combined vaccine logic

TETRAMUNE™

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed and Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate)

Brief Summary

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed and Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate) TETRAMUNE™

For complete Prescribing Information and references, please consult package insert.

INDICATIONS AND USAGE

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed and Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate) TETRAMUNE, is indicated for the active immunization of children 2 months of age to 5 years of age for protection against diphtheria, tetanus, pertussis, and Haemophilus b disease when indications for immunization with DTP vaccine and Haemophilus b Conjugate Vaccine coincide. Typically, this is at 2, 4, 6, and 15 months of age.

As with any vaccine, TETRAMUNE may not protect 100% of individuals receiving the vaccine.

CONTRAINDICATIONS

HYPERSENSITIVITY TO ANY COMPONENT OF THE VACCINE, INCLUDING THIMEROSAL, A MERCURY DERIVATIVE, IS A CONTRAINDICATION.

IMMUNIZATION SHOULD BE DEFERRED DURING THE COURSE OF ANY FEBRILE ILLNESS OR ACUTE INFECTION. THE IMMUNIZATION PRACTICES ADVISORY COMMITTEE (ACIP) HAS STATED THAT "...MINOR ILLNESSES SUCH AS MILD UPPER RESPIRATORY INFECTIONS WITH OR WITHOUT LOW GRADE FEVER ARE NOT CONTRAINDICATIONS."

IMMUNIZATION WITH TETRAMUNE IS CONTRAINDICATED IF THE CHILD HAS EXPERIENCED ANY EVENT FOLLOWING PREVIOUS IMMUNIZATION WITH A PERTUSSIS-CONTAINING VACCINE, WHICH IS CONSIDERED BY THE AAP OR ACIP TO BE A CONTRAINDICATION TO FURTHER DOSES OF PERTUSSIS VACCINE. THESE EVENTS INCLUDE:

AN IMMEDIATE ANAPHYLACTIC REACTION.

ENCEPHALOPATHY OCCURRING WITHIN 7 DAYS FOLLOWING VACCINATION. THIS IS DEFINED AS AN ACUTE, SEVERE CENTRAL-NERVOUS-SYSTEM DISORDER OCCURRING WITHIN 7 DAYS FOLLOWING VACCINATION, AND GENERALLY CONSISTING OF MAJOR ALTERATIONS IN CONSCIOUSNESS, UNRESPONSIVENESS, GENERALIZED OR FOCAL SEIZURES THAT PERSIST MORE THAN A FEW HOURS, WITH FAILURE TO RECOVER WITHIN 24 HOURS.

THE OCCURRENCE OF ANY TYPE OF NEUROLOGICAL SYMPTOMS OR SIGNS, INCLUDING ONE OR MORE CONVULSIONS (SEIZURES) FOLLOWING ADMINISTRATION OF TETRAMUNE IS GENERALLY A CONTRAINDICATION TO FURTHER USE. ANY DECISION TO ADMINISTER SUBSEQUENT DOSES OF A VACCINE CONTAINING DIPHTHERIA, TETANUS, OR PERTUSSIS ANTIGENS SHOULD BE DELAYED UNTIL THE PATIENT'S NEUROLOGICAL STATUS IS BETTER DEFINED.

THE PRESENCE OF ANY EVOLVING OR CHANGING DISORDER AFFECTING THE CENTRAL NERVOUS SYSTEM IS A CONTRAINDICATION TO ADMINISTRATION OF A PERTUSSIS-CONTAINING VACCINE SUCH AS TETRAMUNE REGARDLESS OF WHETHER THE SUSPECTED NEUROLOGICAL DISORDER IS ASSOCIATED WITH OCCURRENCE OF SEIZURE ACTIVITY OF ANY TYPE.

STUDIES HAVE INDICATED THAT A PERSONAL OR FAMILY HISTORY OF SEIZURES IS ASSOCIATED WITH INCREASED FREQUENCY OF SEIZURES FOLLOWING PERTUSSIS IMMUNIZATION.

The ACIP and the AAP recognize certain circumstances in which children with stable central nervous system disorders, including well-controlled seizures or satisfactorily explained single seizures, may receive pertussis vaccine. The ACIP and AAP do not consider a family history of seizures to be a contraindication to pertussis vaccine despite the increased risk of seizures in these individuals.

The decision to administer a pertussis-containing vaccine to children must be made by the physician on an individual basis, with consideration of all relevant factors, and assessment of potential risks and benefits for that individual. The physician should review the full text of ACIP and AAP guidelines prior to considering vaccination for children. The parent or guardian should be advised of the increased risk involved.

There are no data on whether the prophylactic use of antipyretics can decrease the risk of febrile convulsions. However, data suggest that acetaminophen will reduce the incidence of postvaccination fever. The ACIP and AAP suggest administering acetaminophen at age-appropriate doses at the time of vaccination and every 4 to 6 hours to children at higher risk for seizures than the general population.

ROUTINE IMMUNIZATION SHOULD BE DEFERRED DURING AN OUTBREAK OF POLIOMYELITIS PROVIDING THE PATIENT HAS NOT SUSTAINED AN INJURY THAT INCREASES THE RISK OF TETANUS AND PROVIDING AN OUTBREAK OF DIPHTHERIA OR PERTUSSIS DOES NOT OCCUR SIMULTANEOUSLY.

The clinical judgment of the attending physician should prevail at all times.

WARNINGS

THE ACIP STATES THAT IF ANY OF THE FOLLOWING EVENTS OCCUR IN TEMPORAL RELATION TO RECEIPT OF DTP, THE DECISION TO GIVE SUBSEQUENT DOSES OF VACCINE CONTAINING THE PERTUSSIS COMPONENT SHOULD BE CAREFULLY CONSIDERED.

TEMPERATURE OF ≥40.5°C (105°F) WITHIN 48 HOURS NOT DUE TO IDENTIFIABLE CAUSE.

COLLAPSE OR SHOCK-LIKE STATE (HYPOTONIC-HYPORESPONSIVE EPISODE) WITHIN 48 HOURS.

PERSISTENT, INCONSOLABLE CRYING LASTING ≥3 HOURS, OCCURRING WITHIN 48 HOURS.

CONVULSIONS WITH OR WITHOUT FEVER OCCURRING WITHIN 3 DAYS.

"ALTHOUGH THESE EVENTS WERE CONSIDERED ABSOLUTE CONTRAINDICATIONS IN PREVIOUS ACIP RECOMMENDATIONS, THERE MAY BE CIRCUMSTANCES, SUCH AS A HIGH INCIDENCE OF PERTUSSIS, IN WHICH THE POTENTIAL BENEFITS OUTWEIGH POSSIBLE RISKS, PARTICULARLY BECAUSE THESE EVENTS ARE NOT ASSOCIATED WITH PERMANENT SEQUELAE."

IF A CONTRAINDICATION TO ANY OF THE COMPONENTS OF THIS COMBINATION VACCINE EXISTS (SEE **CONTRAINDICATIONS** SECTION), THEN TETRAMUNE SHOULD NOT BE USED. FOR EXAMPLE, IF THERE IS A CONTRAINDICATION AGAINST THE USE OF A PERTUSSIS VACCINE COMPONENT, THEN DIPHTHERIA AND TETANUS TOXOIDS ADSORBED, FOR PEDIATRIC USE (DT), AND HAEMOPHILUS b CONJUGATE VACCINE (DIPHTHERIA CRM_{197} PROTEIN CONJUGATE) HibTITER®, AS SEPARATE INJECTIONS, SHOULD BE SUBSTITUTED FOR EACH OF THE REMAINING DOSES.

THE OCCURRENCE OF SUDDEN INFANT DEATH SYNDROME (SIDS) HAS BEEN REPORTED FOLLOWING ADMINISTRATION OF DTP. HOWEVER, A LARGE CASE-CONTROL STUDY IN THE US REVEALED NO CAUSAL RELATIONSHIP BETWEEN RECEIPT OF DTP VACCINE AND SIDS. A RECENT STUDY OF 6,497 INFANTS IN NORTHERN CALIFORNIA FOUND NO INCREASE IN THE RATE OF SIDS AMONG TETRAMUNE RECIPIENTS.

AS WITH ANY INTRAMUSCULAR INJECTION, TETRAMUNE SHOULD BE GIVEN WITH CAUTION TO INFANTS OR CHILDREN WITH THROMBOCYTOPENIA OR ANY COAGULATION DISORDER THAT WOULD CONTRAINDICATE INTRAMUSCULAR INJECTION (SEE **DRUG INTERACTIONS**).

As reported with Haemophilus b polysaccharide vaccine, cases of Haemophilus type b disease may occur prior to the onset of the protective effect of this vaccine.

TETRAMUNE WILL NOT PROTECT AGAINST *H. INFLUENZAE* OTHER THAN TYPE b STRAINS.

ANTIGENURIA HAS BEEN DETECTED FOLLOWING RECEIPT OF HAEMOPHILUS b CONJUGATE VACCINE AND THEREFORE ANTIGEN DETECTION IN URINE MAY NOT HAVE DIAGNOSTIC VALUE IN SUSPECTED HAEMOPHILUS b DISEASE WITHIN 2 WEEKS OF IMMUNIZATION.

PRECAUTIONS

General: CARE IS TO BE TAKEN BY THE HEALTH CARE PROVIDER FOR SAFE AND EFFECTIVE USE OF THIS PRODUCT.

1. TETRAMUNE is not routinely recommended for immunization of persons older than 5 years of age. Under certain circumstances, TETRAMUNE may be used beyond age 5 years. Because TETRAMUNE contains pediatric DTP vaccine, it is not recommended for use beyond the seventh birthday.
2. PRIOR TO ADMINISTRATION OF ANY DOSE OF TETRAMUNE, THE PARENT OR GUARDIAN SHOULD BE ASKED ABOUT THE PERSONAL HISTORY, FAMILY HISTORY, AND RECENT HEALTH STATUS. THE HEALTH CARE PROVIDER SHOULD ASCERTAIN PREVIOUS IMMUNIZATION HISTORY, CURRENT HEALTH STATUS, AND OCCURRENCE OF ANY SYMPTOMS AND/OR SIGNS OF AN ADVERSE EVENT AFTER PREVIOUS IMMUNIZATIONS, IN THE CHILD TO BE IMMUNIZED, IN ORDER TO DETERMINE THE EXISTENCE OF ANY CONTRAINDICATION TO IMMUNIZATION WITH TETRAMUNE AND TO ALLOW AN ASSESSMENT OF BENEFITS AND RISKS.
3. BEFORE THE INJECTION OF ANY BIOLOGICAL, THE HEALTH CARE PROVIDER SHOULD TAKE ALL PRECAUTIONS KNOWN FOR THE PREVENTION OF ALLERGIC OR ANY OTHER SIDE REACTIONS. This should include: a review of the patient's history regarding possible sensitivity; the ready availability of epinephrine 1:1000 and other appropriate agents used for control of immediate allergic reactions; and a knowledge of the recent literature pertaining to use of the biological concerned, including the nature of side effects and adverse reactions that may follow its use.
4. Children with impaired immune responsiveness, whether due to the use of immunosuppressive therapy (including irradiation, corticosteroids, antimetabolites, alkylating agents, and cytotoxic agents), a genetic defect, human immunodeficiency virus (HIV) infection, or other causes, may have reduced antibody response to active immunization procedures. Deferral of administration of vaccine may be considered in individuals receiving immunosuppressive therapy. Other groups should receive this vaccine according to the usual recommended schedule. (See **DRUG INTERACTIONS**.)
5. This product is not contraindicated based on the presence of human immunodeficiency virus infection.
6. *Since this product is a suspension containing an adjuvant, shake vigorously to obtain a uniform suspension prior to withdrawing each dose from the multiple dose vial.*
7. A separate sterile syringe and needle or a sterile disposable unit should be used for each individual patient to prevent transmission of infectious agents from one person to another. Needles should be disposed of properly and should not be recapped.
8. Special care should be taken to prevent injection into a blood vessel.

National Childhood Vaccine Injury Act: This Act requires that the manufacturer and lot number of the vaccine administered be recorded by the health care provider in the vaccine recipient's permanent medical record (or in a permanent office log or file), along with the date of administration of the vaccine and the name, address, and title of the person administering the vaccine.

The Act further requires the health care provider to report to the Secretary of the Department of Health and Human Services through the Vaccine Adverse Event Reporting System (VAERS) the occurrence following immunization of any event set forth in the Vaccine Injury Table, including: anaphylaxis or anaphylactic shock within 24 hours; encephalopathy or encephalitis within 7 days; shock-collapse or hypotonic-hyporesponsive collapse within 7 days; residual seizure disorder; any acute complication or sequelae (including death) of above events, or any event that would contraindicate further doses of vaccine, according to the package insert for TETRAMUNE.

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed and Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate) TETRAMUNE™

The US Department of Health and Human Services has established VAERS to accept all reports of suspected adverse events after the administration of any vaccine, including but not limited to the reporting of events required by the National Childhood Vaccine Injury Act of 1986. The VAERS toll-free number for VAERS forms and information is 800-822-7967.

Information for Patient: PRIOR TO ADMINISTRATION OF TETRAMUNE, HEALTH CARE PERSONNEL SHOULD INFORM THE PARENT, GUARDIAN, OR OTHER RESPONSIBLE ADULT OF THE RECOMMENDED IMMUNIZATION SCHEDULE FOR PROTECTION AGAINST DIPHTHERIA, TETANUS, PERTUSSIS, AND HAEMOPHILUS b DISEASE AND THE BENEFITS AND RISKS TO THE CHILD RECEIVING THIS VACCINE. GUIDANCE SHOULD BE PROVIDED ON MEASURES TO BE TAKEN SHOULD ADVERSE EVENTS OCCUR, SUCH AS ANTIPYRETIC MEASURES FOR ELEVATED TEMPERATURES AND THE NEED TO REPORT ADVERSE EVENTS TO THE HEALTH CARE PROVIDER. PARENTS SHOULD BE PROVIDED WITH VACCINE INFORMATION PAMPHLETS AT THE TIME OF EACH VACCINATION, AS STATED IN THE NATIONAL CHILDHOOD VACCINE INJURY ACT.

THE HEALTH CARE PROVIDER SHOULD INFORM THE PATIENT, PARENT, OR GUARDIAN OF THE IMPORTANCE OF COMPLETING THE IMMUNIZATION SERIES.

PATIENTS, PARENTS, OR GUARDIANS SHOULD BE INSTRUCTED TO REPORT ANY SERIOUS ADVERSE REACTIONS TO THEIR HEALTH CARE PROVIDER.

Drug Interactions: Children receiving immunosuppressive therapy may have a reduced response to active immunization procedures.

As with other intramuscular injections, TETRAMUNE should be given with caution to children on anticoagulant therapy.

Tetanus Immune Globulin or Diphtheria Antitoxin, if used, should be given in a separate site with a separate needle and syringe.

The AAP recommends that influenza virus vaccine should not be administered within 3 days of immunization with a pertussis-containing vaccine since both vaccines may cause febrile reactions in young children.

Data are not yet available concerning adverse reactions that may occur when TETRAMUNE is given simultaneously with Oral Poliovirus Vaccine (OPV), Measles-Mumps-Rubella (MMR) or Hepatitis B (HB) vaccine at separate sites. Also, data are not available concerning the effects on immune response of OPV, MMR or HB vaccine when TETRAMUNE is given simultaneously. Clinical studies with TETRAMUNE did however allow for the administration of OPV according to the routine immunization schedule for OPV.

Carcinogenesis, Mutagenesis, Impairment of Fertility: TETRAMUNE has not been evaluated for its carcinogenic, mutagenic potential or for impairment of fertility.

Pregnancy: *Pregnancy Category C:* Animal reproduction studies have not been conducted with TETRAMUNE. This product is not recommended for use in individuals 7 years of age or older.

Pediatric Use: The safety and effectiveness of TETRAMUNE in children below the age of 6 weeks have not been established.

For immunization of children 7 years of age or older, Tetanus and Diphtheria Toxoids Adsorbed for Adult Use (Td) is recommended. If contraindication to the pertussis component exists, Diphtheria and Tetanus Toxoids Adsorbed, for Pediatric Use (DT) should be substituted in children who have not reached their seventh birthday.

Full protection against the indicated diseases (tetanus, diphtheria, pertussis, and Haemophilus type b disease) is based on a full course of immunization.

ADVERSE REACTIONS

The safety of TETRAMUNE has been evaluated in 6,793 children at 2, 4, and 6 months of age or at 15 to 18 months of age in three separate sites. The percent of doses administered associated with injection site reactions within 72 hours, or common systemic symptoms within 4 days, is summarized below:

	% of Doses Associated with Symptoms		
	Infants‡ (542 doses)	Infants§ (7269 doses)	Toddlers (107 doses)
Local*			
Erythema	34	19	40
Pain/Tenderness	21	30	65
Swelling	20	20	43
Warmth	16	–	35
Systemic†			
Fever ≥38.0°C	24	40¶	33
Irritability	42	54	49
Drowsiness	26	–	9
Restless sleep	–	28	–
Loss of appetite	–	4	–
Vomiting	5	2	1
Diarrhea	9	1	10
Rash	3	–	0

* within 72 hours of immunization

† within 4 days of immunization

‡ a separate multicenter safety and immunogenicity study, not a subset of the 7269 infant Kaiser study

§ data for this study all collected within 24 hours of immunization (percentages calculated from a range of 7269 to 7500 doses) in the Kaiser Permanente Safety and Immunogenicity Study

¶ perceived fever

Based on review of the Kaiser-Permanente Medical Care Program utilization data base of hospitalizations (within 60 days) and emergency room visits (within 30 days of immunization) in 6,497 infants who received TETRAMUNE, the most common reasons for seeking care include: trauma, viral illness, and respiratory illnesses (eg, upper respiratory infection, otitis media, bronchitis/bronchiolitis, and pneumonia). One child who received TETRAMUNE became transiently pale and tremulous without loss of responsiveness 4 hours after immunization and was hospitalized with a diagnosis of seizure. No other hospital visits for seizure or hypotonic, hyporesponsive episodes were reported within 72 hours of immunization. These results were not different from those observed in 3,935 infants who received DTP and HbOC at separate injection sites.

As with other aluminum-containing vaccines, a nodule may occasionally be palpable at the injection site for several weeks. Although not seen in studies with TETRAMUNE, sterile abscess formation or subcutaneous atrophy at the injection site may also occur.

The following significant adverse events have occurred following administration of DTP vaccines: persistent, inconsolable crying ≥3 hours (1/100 doses), high-pitched, unusual crying (1/1000 doses), fever ≥40.5°C (105°F) (1/330 doses), transient shock-like (hypotonic, hyporesponsive) episode (1/1750 doses), convulsions (1/1750 doses).

The ACIP states: "Although DTP may rarely produce symptoms that some have classified as acute encephalopathy, a causal relation between DTP vaccine and permanent brain damage has not been demonstrated. If the vaccine ever causes brain damage, the occurrence of such an event must be exceedingly rare. A similar conclusion has been reached by the Committee on Infectious Diseases of the American Academy of Pediatrics, the Child Neurology Society, the Canadian National Advisory Committee on Immunization, the British Joint Committee on Vaccination and Immunization, the British Pediatric Association, and the Institute of Medicine."

The occurrence of sudden infant death syndrome (SIDS) has been reported following administration of DTP. However, a large case-control study in the US revealed no causal relationship between receipt of DTP vaccine and SIDS. A recent study of 6,497 infants in northern California found no increase in the rate of SIDS among TETRAMUNE recipients.

Onset of infantile spasms has occurred in infants who have recently received DTP or DT. Analysis of data from the National Childhood Encephalopathy Study on children with infantile spasms showed that receipt of preparations containing diphtheria, tetanus, and/or pertussis antigens was not causally related to infantile spasms. The incidence of onset of infantile spasms increases at 3 to 9 months of age, the time period in which the second and third doses of DTP are generally given. Therefore, some cases of infantile spasms can be expected to be related by chance alone to recent receipt of vaccines containing DTP.

Bulging fontanel has been reported after DTP immunization, although no cause and effect relationship has been established.

Cardiac effects and respiratory difficulties, including apnea, have been reported rarely following DTP immunization.

Other events that have been reported following administration of vaccines containing diphtheria, tetanus, pertussis, or Haemophilus b antigens include: urticaria, erythema multiforme or other rash, arthralgias, and, more rarely, a severe anaphylactic reaction (eg, urticaria with swelling of the mouth, difficulty breathing, hypotension, or shock) and neurological complications, such as convulsions, encephalopathy, and various mono- and polyneuropathies, including Guillain-Barré syndrome. Permanent neurological disability and death have also been reported rarely in temporal relation to immunization although a causal relationship has not been established.

DOSAGE AND ADMINISTRATION

For Intramuscular Use Only.

See **DOSAGE AND ADMINISTRATION** in full Prescribing Information for complete dosing and precautionary information.

Manufactured by
LEDERLE LABORATORIES
A Division of American Cyanamid Company
Pearl River, NY 10965

and

PRAXIS BIOLOGICS, INC.
A Subsidiary of American Cyanamid Company
West Henrietta, NY 14586

Distributed by
LEDERLE-PRAXIS BIOLOGICALS
A Division of American Cyanamid Company
Wayne, NJ 07470

REV. 3/93
L-32092-93

NEW LOW-DOSE

LOZOL® 1.25 MG
INDAPAMIDE TABLETS

A LITTLE MEANS A LOT

TO THE OLDER PATIENT WITH MILD TO MODERATE HYPERTENSION

Efficacy comparable to higher doses of indapamide with the benefits of a lower once-daily dose[1*]

Favorable metabolic profile[†] — no effect on lipids, only 2% incidence of clinical hypokalemia[‡]

Less patient discontinuation than with placebo

Side-effect profile compatible with other antihypertensive agents

Please see brief summary of prescribing information on this page.

LOZOL® (indapamide) 1.25 mg and 2.5 mg tablets
BRIEF SUMMARY

INDICATIONS: LOZOL (indapamide) is indicated for the treatment of hypertension, alone or in combination with other antihypertensive drugs, and for the treatment of salt and fluid retention associated with congestive heart failure.
Usage in Pregnancy: See PRECAUTIONS.

CONTRAINDICATIONS: Anuria, hypersensitivity to indapamide or other sulfonamide-derived drugs.

WARNINGS: Infrequent cases of severe hyponatremia, accompanied by hypokalemia, have been reported with 2.5 mg and 5.0 mg indapamide primarily in elderly females. Symptoms were reversed by electrolyte replenishment. Hyponatremia considered possibly clinically significant (<125 mEq/L) has not been observed in clinical trials with the 1.25 mg dosage (see PRECAUTIONS). Hypokalemia occurs commonly with diuretics (**see ADVERSE REACTIONS, hypokalemia**), and electrolyte monitoring is essential. In general, diuretics should not be given with lithium.

PRECAUTIONS: Perform serum electrolyte determinations at appropriate intervals, especially in patients who are vomiting excessively or receiving parenteral fluids, in patients subject to electrolyte imbalance, or in patients on a salt-restricted diet. In addition, patients should be observed for clinical signs of fluid or electrolyte imbalance, such as hyponatremia, hypochloremic alkalosis, or hypokalemia. The risk of hypokalemia secondary to diuresis and natriuresis is increased with larger doses, with brisk diuresis, with severe cirrhosis, and with concomitant use of corticosteroids or ACTH. Interference with adequate oral intake of electrolytes will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis, such as increased ventricular irritability.
Dilutional hyponatremia may occur in edematous patients; appropriate treatment is usually water restriction. In actual salt depletion, appropriate replacement is the treatment of choice. Chloride deficit is usually mild, not requiring specific treatment except in extraordinary circumstances (liver, renal disease).
Hyperuricemia may occur, and frank gout may be precipitated in certain patients receiving indapamide. Serum concentrations of uric acid should be monitored periodically.
Use with caution in patients with severe renal disease; consider withholding or discontinuing if progressive renal impairment is observed. Renal function tests should be performed periodically.
Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
Latent diabetes may become manifest and insulin requirements in diabetic patients may be altered during thiazide administration. A mean increase in glucose of 6.47 mg/dL was observed in patients treated with indapamide 1.25 mg, which was not considered clinically significant in these trials. Serum concentrations of glucose should be monitored routinely during treatment with indapamide.
Calcium excretion is decreased by diuretics pharmacologically related to indapamide. After six to eight weeks of indapamide 1.25 mg treatment and in long-term studies of hypertensive patients with higher doses of indapamide, however, serum concentrations of calcium increased only slightly with indapamide. Indapamide may decrease serum PBI levels without signs of thyroid disturbance. Complications of hyperparathyroidism have not been seen. Discontinue before tests of parathyroid function are performed.
Thiazides have exacerbated or activated systemic lupus erythematosus. Consider this possibility with indapamide.

DRUG INTERACTIONS: LOZOL may add to or potentiate the action of other antihypertensive drugs. The antihypertensive effect of the drug may be enhanced in the postsympathectomized patient. Indapamide may decrease arterial responsiveness to norepinephrine, but this does not preclude the use of norepinephrine.
In mouse and rat lifetime carcinogenicity studies, there were no significant differences in the incidence of tumors between the indapamide-treated animals and the control groups.
Pregnancy Category B: Diuretics cross the placental barrier and appear in cord blood. Indapamide should be used during pregnancy only if clearly needed. Use may be associated with fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse effects that have occurred in adults. It is not known whether this drug is excreted in human milk. If use of this drug is deemed essential, the patient should stop nursing.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. From Phase I/III placebo-controlled studies with indapamide 1.25 mg, adverse reactions with ≥5% cumulative incidence: headache, infection, pain, back pain, dizziness, rhinitis; <5% cumulative incidence: asthenia, flu syndrome, abdominal pain, chest pain, constipation, diarrhea, dyspepsia, nausea, peripheral edema, nervousness, hypertonia, cough, pharyngitis, sinusitis, conjunctivitis. All other clinical adverse reactions occurred at an incidence of <1%. In controlled clinical trials of six to eight weeks in duration, 20% of patients receiving indapamide 1.25 mg, 61% of patients receiving indapamide 5.0 mg, and 80% of patients receiving indapamide 10.0 mg had at least one potassium value below 3.4 mEq/L. In the indapamide 1.25 mg group, about 40% of those patients who reported hypokalemia as a laboratory adverse event returned to normal serum potassium values without intervention. Hypokalemia with concomitant clinical signs or symptoms occurred in 2% of patients receiving indapamide 1.25 mg. From Phase II placebo-controlled studies and long-term controlled clinical trials with LOZOL 2.5 mg or 5.0 mg, adverse reactions with ≥ 5% cumulative incidence: headache, dizziness, fatigue, weakness, loss of energy, lethargy, tiredness or malaise, muscle cramps or spasm or numbness of the extremities, nervousness, tension, anxiety, irritability or agitation; <5% cumulative incidence: lightheadedness, drowsiness, vertigo, insomnia, depression, blurred vision, constipation, nausea, vomiting, diarrhea, gastric irritation, abdominal pain or cramps, anorexia, orthostatic hypotension, premature ventricular contractions, irregular heart beat, palpitations, frequency of urination, nocturia, polyuria, rash, hives, pruritus, vasculitis, impotence or reduced libido, rhinorrhea, flushing, hyperuricemia, hyperglycemia, hyponatremia, hypochloremia, increase in serum BUN or creatinine, glycosuria, weight loss, dry mouth, tingling of extremities. Hypokalemia with concomitant clinical signs or symptoms occurred in 3% of patients receiving indapamide 2.5 mg q.d. and 7% of patients receiving indapamide 5 mg q.d. In long-term controlled clinical trials comparing the hypokalemic effects of daily doses of indapamide and hydrochlorothiazide, however, 47% of patients receiving indapamide 2.5 mg, 72% of patients receiving indapamide 5 mg, and 44% of patients receiving hydrochlorothiazide 50 mg had at least one potassium value (out of a total of 11 taken during the study) below 3.5 mEq/L. In the indapamide 2.5 mg group, over 50% of those patients returned to normal serum potassium values without intervention. Other adverse reactions reported with antihypertensive/diuretics are intrahepatic cholestatic jaundice, sialadenitis, xanthopsia, photosensitivity, purpura, bullous eruptions, Stevens-Johnson syndrome, necrotizing angiitis, fever, respiratory distress (including pneumonitis), anaphylactic reactions, agranulocytosis, leukopenia, thrombocytopenia, aplastic anemia.

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.
Keep tightly closed. Store at controlled room temperature, 15°-30°C (59°-86°F). Avoid excessive heat. Dispense in tight containers as defined in USP.
See product circular for full prescribing information.
Revised: April 1993

* In a controlled clinical trial, at 8 weeks the change in supine diastolic BP with 5 mg of indapamide was -10.8 mm Hg vs. -8.8 mm Hg with LOZOL 1.25 mg.

† Because of the diuretic effects of LOZOL 1.25, changes in certain electrolytes and blood chemistries can occur. Serum electrolytes and blood chemistries should therefore be monitored.

‡ 19.6% of patients had values less than 3.4 mEq/L. Only 7.5% had potassium levels below 3.2 mEq/L and less than 1% fell below 3.0 mEq/L. Metabolic changes at higher doses of indapamide may be greater.

Reference: 1. Data on file, Rhône-Poulenc Rorer Pharmaceuticals Inc.

RHÔNE-POULENC RORER

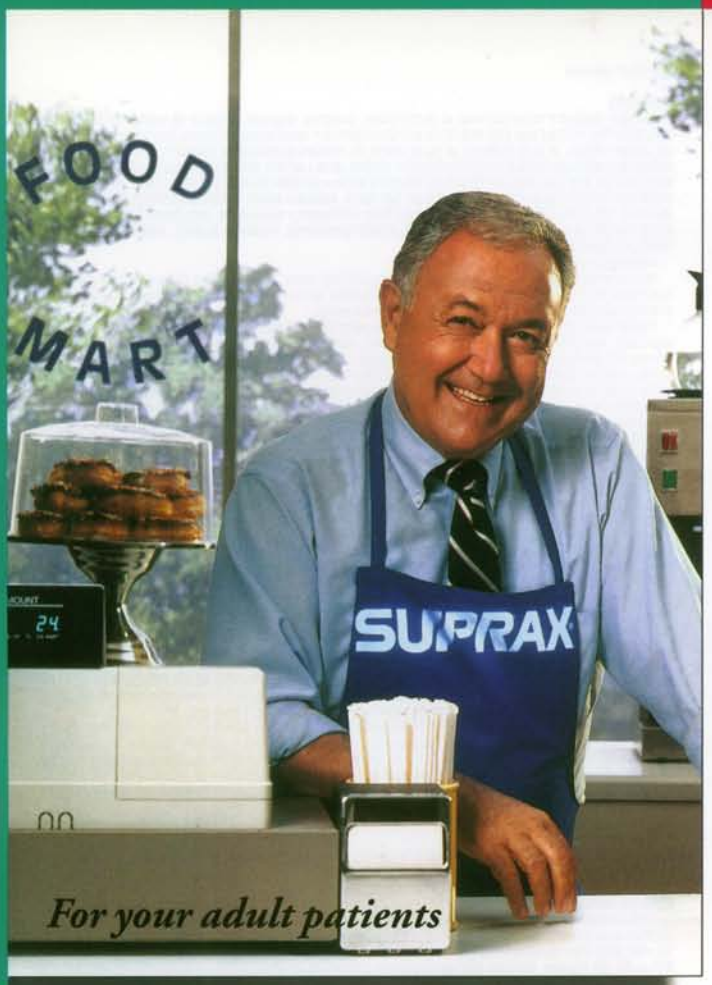
RHÔNE-POULENC RORER PHARMACEUTICALS INC.
500 ARCOLA ROAD
COLLEGEVILLE, PA 19426

LZ70M793(1)A 7/93 FC# 93-R70

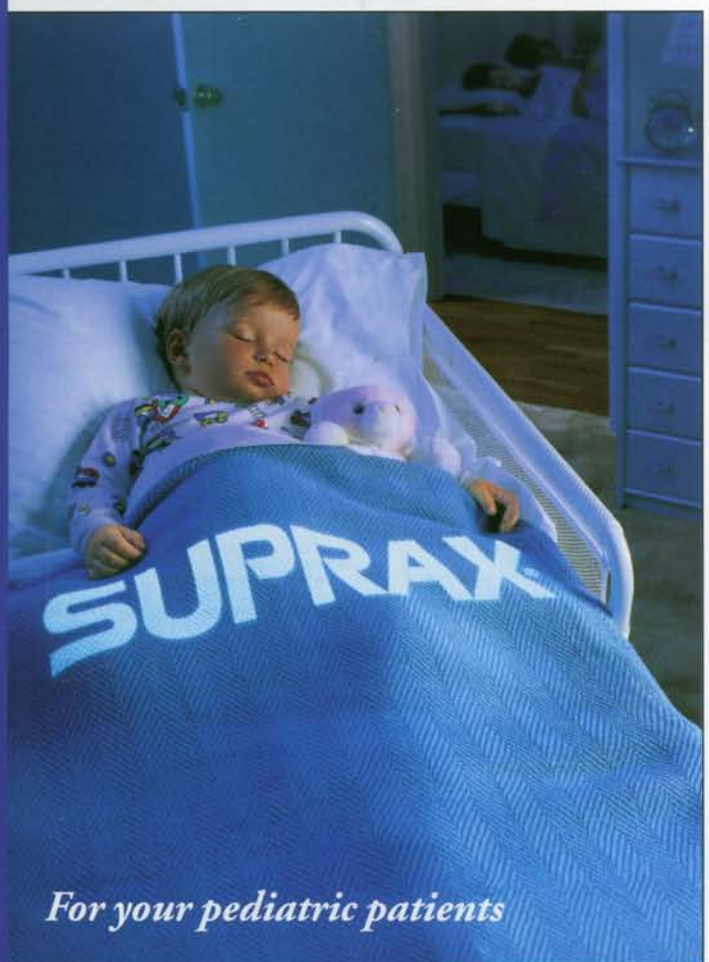
the treatment groups (for a rate of 30.7 per 1000 patients) and 518 coronary events among 15 165 patients in the control groups (for a rate of 34.2 per 1000). The difference in rates was thus 3.5 per 1000; and 3.5÷34.2=10.2%. Baseline diastolic blood pressures were 85 to 109 mm Hg among these 30 403 patients, with an average baseline diastolic blood pressure of 97.5 mm Hg. Collins et al[6] also indicate that the difference in major coronary events between treatment and control groups was statistically significant. Whether this effect is clinically worthwhile is debatable, but I think that the numbers speak for themselves in demonstrating a 10% short-term (5-year) reduction in the risk for MI associated with the treatment of mild hypertension with drugs. A key question still unanswered is what effects longer periods of antihypertensive treatment have on the risk for MI and on cardiac mortality.

Kevin A. Pearce, MD, MPH
Bowman Gray School of Medicine
Winston-Salem, NC

1. Hypertension Detection and Follow-up Program Cooperative Group. Five-year findings of the Hypertension Detection and Follow-up Program, I: reduction in mortality of persons with high blood pressure, including mild hypertension. *JAMA.* 1979;242:2562-2571.
2. Report by the Management Committee. The Australian therapeutic trial in mild hypertension. *Lancet.* 1980;1:1261-1267.
3. Helgeland A. Treatment of mild hypertension: a five year controlled drug trial. *Am J Med.* 1980;69:725-732.
4. VA/NHLBI Study Group for Evaluating Treatment in Mild Hypertension. Evaluation of treatment in mild hypertension: VA/NHLBI feasibility trial. *Ann N Y Acad Sci.* 1978;304:267-268.
5. Medical Research Council Working Party. MRC trial of treatment of mild hypertension: principal results. *BMJ.* 1985;291:97-104.
6. Collins J, Peto R, MacMahon S, et al. Blood pressure, stroke, and coronary heart disease, II: short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet.* 1990;335:827-838.
7. MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke, and coronary heart disease, I: prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet.* 1990;335:765-774.



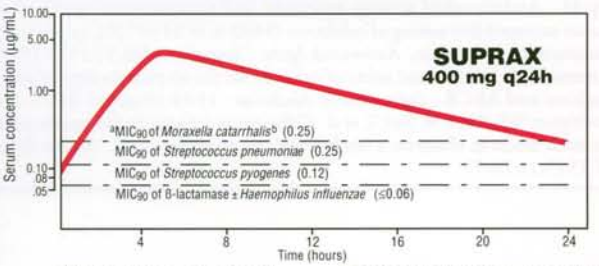
For your adult patients



For your pediatric patients

Working Continuously 24 Hours a Day... Once a Day

SUPRAX maintains inhibitory concentrations above MIC_{90} for virtually 24 hours[1]*



[a] MIC_{90} values from Jones and Barry.[2] [b] 17 of 20 strains were ß-lactamase producing.

Proven Clinical Efficacy

In Bronchitis[3†]
Cured: 67%
Improved: 29%
96% (n=8,993)

In Pharyngitis/ Tonsillitis[1†]
Cured: 89%
Improved: 10%
99% (n=300)

In Otitis Media[4†]
97% cured/improved (n=29)

*Although a useful guide, *in vitro* activity does not necessarily correlate with clinical response.

†Due to indicated susceptible organisms.

ONCE-A-DAY
SUPRAX®
cefixime
TABLETS 400 mg
ORAL SUSPENSION 100 mg/5 mL

Working 24 hours a day

Please see brief summary of Prescribing Information on adjacent page for WARNINGS, ADVERSE REACTIONS, and CONTRAINDICATIONS. GI side effects are the most frequently reported adverse effects.

SUPRAX is administered as a single dose, once a day, or if preferred, in equally divided doses twice a day.

ONCE-A-DAY SUPRAX®

cefixime

TABLETS
400 mg
ORAL SUSPENSION
100 mg/5 mL

Working 24 hours a day

References: 1. Data on file. Lederle Laboratories, Pearl River, NY. **2.** Jones RN, Barry AL. Antimicrobial activity, spectrum, and recommendations for disk diffusion susceptibility testing of ceftibuten (7432-S; SCH 39720), a new orally administered cephalosporin. *Antimicrob Agents Chemother.* 1988;32:1576-1582. **3.** Stratton CW. Efficacy and safety of cefixime for the empiric therapy of acute bronchitis and AECB. *Infections in Medicine.* 1993;10(suppl B):11-15. **4.** Rodriguez WJ, Khan W, Sait T, et al. Cefixime *vs.* cefaclor in the treatment of acute otitis media in children: a randomized, comparative study. *Pediatr Infect Dis J.* 1993;12:70-74.

Brief Summary

SUPRAX®
Cefixime
Oral

Please see package insert for full Prescribing Information.

INDICATIONS AND USAGE

SUPRAX is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Uncomplicated Urinary Tract Infections caused by *Escherichia coli* and *Proteus mirabilis*.

Otitis Media caused by *Haemophilus influenzae* (beta-lactamase positive and negative strains), *Moraxella (Branhamella) catarrhalis*, (most of which are beta-lactamase positive), and *Streptococcus pyogenes*.*

Note: For information on otitis media caused by *Streptococcus pneumoniae*, see **CLINICAL STUDIES** section.

Pharyngitis and Tonsillitis, caused by *S pyogenes*.

Note: Penicillin is the usual drug of choice in the treatment of *S pyogenes* infections, including the prophylaxis of rheumatic fever. SUPRAX is generally effective in the eradication of *S pyogenes* from the nasopharynx; however, data establishing the efficacy of SUPRAX in the subsequent prevention of rheumatic fever are not available.

Acute Bronchitis and Acute Exacerbations of Chronic Bronchitis, caused by *S pneumoniae* and *H influenzae* (beta-lactamase positive and negative strains).

Uncomplicated Gonorrhea (Cervical/Urethral), caused by *Neisseria gonorrhoeae* (penicillinase- and nonpenicillinase-producing strains).

Appropriate cultures and susceptibility studies should be performed to determine the causative organism and its susceptibility to SUPRAX; however, therapy may be started while awaiting the results of these studies. Therapy should be adjusted, if necessary, once these results are known.

*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

CLINICAL STUDIES

In clinical trials of otitis media in nearly 400 children between the ages of 6 months to 10 years, *S pneumoniae* was isolated from 47% of the patients, *H influenzae* from 34%, *M (B) catarrhalis* from 15%, and *S pyogenes* from 4%.

The overall response rate of *S pneumoniae* to cefixime was approximately 10% lower and that of *H influenzae* or *M (B) catarrhalis* approximately 7% higher (12% when beta-lactamase positive strains of *H influenzae* are included) than the response rates of these organisms to the active control drugs.

In these studies, patients were randomized and treated with either cefixime at dose regimens of 4 mg/kg BID or 8 mg/kg QD, or with a standard antibiotic regimen. Sixty-nine percent to 70% of the patients in each group had resolution of signs and symptoms of otitis media when evaluated 2 to 4 weeks posttreatment, but persistent effusion was found in 15% of the patients. When evaluated at the completion of therapy, 17% of patients receiving cefixime and 14% of patients receiving effective comparative drugs (18% including those patients who had *H influenzae* resistant to the control drug and who received the control antibiotic) were considered to be treatment failures. By the 2- to 4-week follow-up, a total of 30% to 31% of patients had evidence of either treatment failure or recurrent disease.

Bacteriological Outcome of Otitis Media at 2 to 4 Weeks Posttherapy
Based on Repeat Middle Ear Fluid Culture or
Extrapolation from Clinical Outcome

Organism	Cefixime[a] 4 mg/kg BID	Cefixime[a] 8 mg/kg QD	Control[a] drugs
Streptococcus pneumoniae	48/70 (69%)	18/22 (82%)	82/100 (82%)
Haemophilus influenzae beta-lactamase negative	24/34 (71%)	13/17 (76%)	23/34 (68%)
Haemophilus influenzae beta-lactamase positive	17/22 (77%)	9/12 (75%)	1/1[b]
Moraxella (Branhamella) catarrhalis	26/31 (84%)	5/5	18/24 (75%)
S pyogenes	5/5	3/3	6/7
All Isolates	120/162 (74%)	48/59 (81%)	130/166 (78%)

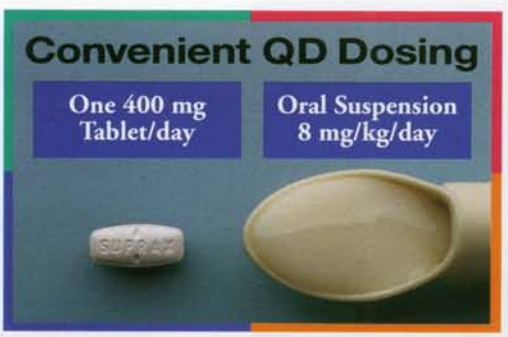
[a] Number eradicated/number isolated.

[b] An additional 20 beta-lactamase positive strains of *H influenzae* were isolated, but were excluded from this analysis because they were resistant to the control antibiotic. In 19 of these, the clinical course could be assessed, and a favorable outcome occurred in 10. When these cases are included in the overall bacteriological evaluation of therapy with the control drugs, 140/185 (76%) of pathogens were considered to be eradicated.

Tablets should not be substituted for suspension when treating otitis media.

CONTRAINDICATIONS

SUPRAX is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.



SUPRAX® cefixime

WARNINGS

BEFORE THERAPY WITH SUPRAX IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO SUPRAX OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Administer cautiously to allergic patients.

Treatment with broad-spectrum antibiotics, including SUPRAX, alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of severe antibiotic-associated diarrhea including pseudomembranous colitis.

Pseudomembranous colitis has been reported with the use of SUPRAX and other broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins); therefore, it is important to consider this diagnosis in patients who develop diarrhea in association with the use of antibiotics. Symptoms of pseudomembranous colitis may occur during or after antibiotic treatment and may range in severity from mild to life-threatening. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, management should include fluids, electrolytes, and protein supplementation. If the colitis does not improve after the drug has been discontinued, or if the symptoms are severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes of colitis should be excluded.

PRECAUTIONS

General: Use, especially when prolonged, may result in overgrowth of resistant organisms. If superinfection occurs during therapy, take appropriate measures.

Carefully monitor patients on dialysis. Adjust dosage of SUPRAX in patients with renal impairment and those undergoing continuous ambulatory peritoneal dialysis and hemodialysis. (See **DOSAGE AND ADMINISTRATION** in package insert.)

Prescribe cautiously in patients with a history of gastrointestinal disease, particularly colitis.

Drug Interactions: No significant drug interactions have been reported to date.

Drug/Laboratory Test Interactions: A false-positive reaction for ketones in the urine may occur with tests using nitroprusside but not with those using nitroferricyanide.

SUPRAX administration may result in a false-positive reaction for glucose in the urine using Clinitest®,** Benedict's solution, or Fehling's solution. Use glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix®** or Tes-Tape®**).

A false-positive direct Coombs test has been reported during treatment with other cephalosporin antibiotics; therefore, it should be recognized that a positive Coombs test may be due to the drug.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Although no lifetime animal studies have been conducted to evaluate carcinogenic potential, no mutagenic potential of SUPRAX was found in standard laboratory tests. In rats, reproductive studies revealed no fertility impairment at doses up to 125 times the adult therapeutic dose.

Usage in Pregnancy: *Pregnancy Category B:* Reproduction studies have been performed in mice and rats at doses up to 400 times the human dose and have revealed no evidence of harm to the fetus due to SUPRAX. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: SUPRAX has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.

Nursing Mothers: It is not known whether SUPRAX is excreted in human milk. Consider discontinuing nursing temporarily during treatment with this drug.

Pediatric Use: Safety and effectiveness of SUPRAX in children aged less than 6 months have not been established.

The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pediatric patients receiving the suspension was comparable to that seen in adult patients receiving tablets.

ADVERSE REACTIONS

Most adverse reactions observed in clinical trials were of a mild and transient nature. Five percent (5%) of patients in the US trials discontinued therapy because of drug-related adverse reactions. The most commonly seen adverse reactions in US trials of the tablet formulation were gastrointestinal events, which were reported in 30% of adult patients on either the BID or the QD regimen. Clinically mild gastrointestinal side effects occurred in 20% of all patients, moderate events occurred in 9% of all patients, and severe adverse reactions occurred in 2% of all patients. Individual event rates included diarrhea 16%, loose or frequent stools 6%, abdominal pain 3%, nausea 7%, dyspepsia 3%, and flatulence 4%. The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pediatric patients receiving the suspension was comparable to that seen in adult patients receiving tablets.

These symptoms usually responded to symptomatic therapy or ceased when SUPRAX was discontinued.

Several patients developed severe diarrhea and/or documented pseudomembranous colitis, and a few required hospitalization.

The following adverse reactions have been reported following the use of SUPRAX. Incidence rates were less than 1 in 50 (less than 2%), except as noted above for gastrointestinal events.

Gastrointestinal: Diarrhea, loose stools, abdominal pain, dyspepsia, nausea, and vomiting. Several cases of documented pseudomembranous colitis were identified during the studies. The onset of pseudomembranous colitis symptoms may occur during or after therapy.

Hypersensitivity Reactions: Skin rashes, urticaria, drug fever, and pruritus. Erythema multiforme, Stevens-Johnson syndrome, and serum sickness-like reactions have been reported.

Hepatic: Transient elevations in SGPT, SGOT, and alkaline phosphatase.

Renal: Transient elevations in BUN or creatinine.

Central Nervous System: Headaches or dizziness.

Hemic and Lymphatic Systems: Transient thrombocytopenia, leukopenia, and eosinophilia. Prolongation in prothrombin time was seen rarely.

Other: Genital pruritus, vaginitis, candidiasis.

The following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Adverse Reactions: Allergic reactions including anaphylaxis, toxic epidermal necrolysis, superinfection, renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage, and colitis.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see **DOSAGE AND ADMINISTRATION** and **OVERDOSAGE**). If seizures associated with drug therapy occur, discontinue drug. Administer anticonvulsant therapy if clinically indicated.

Abnormal Laboratory Tests: Positive direct Coombs test, elevated bilirubin, elevated LDH, pancytopenia, neutropenia, agranulocytosis.

OVERDOSAGE

Gastric lavage may be indicated; otherwise, no specific antidote exists. Cefixime is not removed in significant quantities from the circulation by hemodialysis or peritoneal dialysis. Adverse reactions in small numbers of healthy adult volunteers receiving single doses up to 2 g of SUPRAX did not differ from the profile seen in patients treated at the recommended doses.

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Williams & Wilkins 428 East Preston Street, Baltimore, MD 21202

Ismo® (isosorbide mononitrate) **20 mg tablets**

BRIEF SUMMARY (*FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR.*)

Indications and Usage
Ismo is indicated for prevention of angina pectoris due to coronary artery disease. The onset of action is not rapid enough for it to be useful in aborting an acute anginal episode.

Clinical Pharmacology
Isosorbide mononitrate is the major active metabolite of isosorbide dinitrate; most of the clinical activity of the dinitrate comes from the mononitrate. Ismo is not subject to first-pass metabolism in the liver and the absolute bioavailability of isosorbide mononitrate from Ismo tablets is nearly 100%. The rate of clearance of Ismo is the same in healthy young adults, in patients with various degrees of renal, hepatic, or cardiac dysfunction, and in the elderly.

Several well-controlled studies have demonstrated that active nitrates were indistinguishable from placebo after 24 hours (or less) of continuous therapy due to the development of tolerance. Only after nitrates are absent from the body for several hours is their antianginal efficacy restored.

The drug-free interval sufficient to avoid tolerance to isosorbide mononitrate is not completely defined. The only regimen shown to avoid development of tolerance with isosorbide mononitrate involves two daily doses of Ismo tablets given 7 hours apart, so there is a gap of 17 hours between the second dose of each day and the first dose of the next day. Taking account of the relatively long half-life of isosorbide mononitrate this result is consistent with those obtained for other organic nitrates.

The same twice-daily regimen of Ismo tablets successfully avoided significant rebound/withdrawal effects. In studies of other nitrates, the incidence and magnitude of such phenomena appear to be highly dependent upon the schedule of nitrate administration.

Contraindications
Allergic reactions are extremely rare, but do occur. Ismo is contraindicated in patients allergic to it.

Warnings
Because the effects of Ismo are difficult to terminate rapidly and have not been established in patients with acute myocardial infarction (MI) or congestive heart failure (CHF), this drug is not recommended in these patients. If Ismo is used in these patients, careful clinical or hemodynamic monitoring is required to avoid the hazards of hypotension and tachycardia.

Precautions
GENERAL
Severe hypotension, particularly with upright posture, may occur with even small doses. Therefore, use with caution in patients who may be volume depleted or who are already hypotensive. Paradoxical bradycardia and increased angina pectoris may accompany Ismo-induced hypotension.

Nitrates may aggravate angina caused by hypertrophic cardiomyopathy.

INFORMATION FOR PATIENTS
Tell patients they must carefully follow the prescribed dosing schedule (2 doses taken 7 hours apart) to maintain the antianginal effect (eg, take first dose on awakening and second dose 7 hours later).

Daily headaches sometimes accompany treatment with nitrates, including Ismo, and are a marker of drug activity. Patients with headaches should not alter their treatment schedule since loss of headache may be associated with simultaneous loss of antianginal efficacy. Headaches may be treated with aspirin and/or acetaminophen without affecting the antianginal activity of Ismo.

Light-headedness on standing, especially just after rising from a recumbent or seated position, may occur. This may be more frequent in patients who have consumed alcohol.

DRUG INTERACTIONS
Vasodilating effects of Ismo may be additive with those of other vasodilators, especially alcohol.

Marked symptomatic orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustments of either class of agents may be necessary.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
No carcinogenic effects were observed in mice or rats exposed to oral Ismo, nor were adverse effects on rat fertility observed.

No mutagenic activity was seen in *in vitro* or *in vivo* assays.

PREGNANCY CATEGORY C
Ismo has been shown to have embryocidal effects in rats and rabbits at doses at least 70 times the maximum human dose. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if potential benefit justifies potential fetal risk.

NURSING MOTHERS
Excretion in human milk is unknown. Use caution if administered to a nursing woman.

PEDIATRIC USE
Safety and effectiveness have not been established.

Adverse Reactions
Frequency of Adverse Reactions (Discontinuations)* Occurring in >1% of Subjects

	6 Controlled U.S. Studies		92 Clinical Studies
Dose	Placebo	20 mg	(varied)
Patients	204	219	3344
Headache	9% (0%)	38% (9%)	19% (4.3%)
Dizziness	1% (0%)	5% (1%)	3% (0.2%)
Nausea, Vomiting	<1% (0%)	4% (3%)	2% (0.2%)

*Some individuals discontinued for multiple reasons

Fewer than 1% of patients reported each of the following (in many cases a causal relationship is uncertain): *Cardiovascular;* angina pectoris, arrhythmias, atrial fibrillation, hypotension, palpitations, postural hypotension, premature ventricular contractions, supraventricular tachycardia, syncope. *Dermatologic;* pruritus, rash. *Gastrointestinal;* abdominal pain, diarrhea, dyspepsia, tenesmus, tooth disorder, vomiting. *Genitourinary;* dysuria, impotence, urinary frequency. *Miscellaneous;* asthenia, blurred vision, cold sweat, diplopia, edema, malaise, neck stiffness, rigors. *Musculoskeletal;* arthralgia. *Neurologic;* agitation, anxiety, confusion, dyscoordination, hypoesthesia, hypokinesia, increased appetite, insomnia, nervousness, nightmares. *Respiratory;* bronchitis, pneumonia, upper respiratory tract infection.

Rarely, ordinary doses of organic nitrates have caused methemoglobinemia in normal-seeming patients (See **Overdosage**).

Overdosage
The ill effects of overdosage are generally related to the ability of Ismo to induce vasodilatation, venous pooling, reduced cardiac output and hypotension. Symptoms may include increased intracranial pressure, with any or all of persistent throbbing headache, confusion, and moderate fever; vertigo; palpitations; visual disturbances; nausea and vomiting (possibly with colic and even bloody diarrhea); syncope (especially with upright posture); air hunger and dyspnea, later followed by reduced ventilatory effort; diaphoresis, with the skin either flushed or cold and clammy; heart block and bradycardia; paralysis; coma; seizures and death.

Serum levels have no role in managing overdose. The likely lethal dose in humans is unknown.

There is neither a specific antidote to Ismo overdose, nor data to suggest a means for accelerating its elimination from the body; dialysis is ineffective. Hypotension associated with Ismo overdose results from venodilatation and arterial hypovolemia; therefore, direct therapy toward an increase in central fluid volume. Use of arterial vasoconstrictors (eg, epinephrine) is likely to do more harm than good. In patients with renal disease or CHF, treatment of Ismo overdose may be difficult and require invasive monitoring.

Methemoglobinemia has occurred in patients receiving other organic nitrates, and probably could occur as a side effect of Ismo. There are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible. Suspect the diagnosis in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO_2. Classically, methemoglobinemic blood is chocolate brown, without color change on exposure to air. The treatment of choice for methemoglobinemia is methylene blue, 1-2 mg/kg intravenously.

DOSAGE AND ADMINISTRATION
The recommended regimen of Ismo tablets is 20 mg (one tablet) twice daily, with the two doses given 7 hours apart. For most patients, this can be accomplished by taking the first dose on awakening and the second dose 7 hours later. This dosing regimen provides a daily nitrate-free interval to avoid the development of refractory tolerance (see **Clinical Pharmacology**).

Well-controlled studies have shown that tolerance to Ismo tablets is avoided when using the twice daily regimen in which the two doses are given 7 hours apart. This regimen has been shown to have antianginal efficacy beginning 1 hour after the first dose and lasting at least 5 hours after the second dose. The duration (if any) of antianginal activity beyond 12 hours has not been studied; large controlled studies with other nitrates suggest that no dosing regimen should be expected to provide more than 12 hours of continuous antianginal efficacy per day.

Dosage adjustments are not necessary in the elderly patients or in patients with altered renal or hepatic function.

This Brief Summary is based upon the current Ismo direction circular, CI 4130-2, Revised October 20, 1992.

***References:* 1.** *Data on file, Wyeth-Ayerst Laboratories, Protocol 12.*
2. *Friedman RG, et al: Comparative clinical trial of isosorbide mononitrate and isosorbide dinitrate in patients with stable angina pectoris.* J Invas Cardiol *1992;4:319-329.*

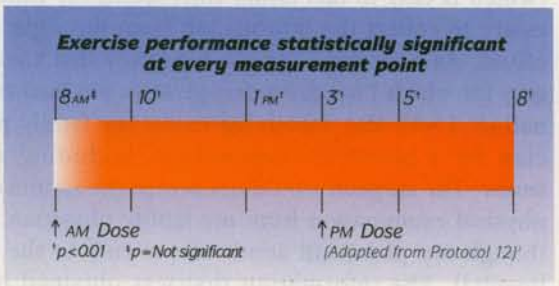
A·H·ROBINS BOEHRINGER MANNHEIM PHARMACEUTICALS WYETH-AYERST LABORATORIES

60376

Ismo® 20 mg tablets
(isosorbide mononitrate)

Activity You Can Count On

Antianginal activity during the active hours[1]*



This study measured improvement in exercise performance to moderately severe anginal pain in patients given Ismo 20 mg (N = 56) or placebo (N = 60) dosed at 8 AM and 3 PM for 2 weeks following a 1-week washout period.

Effective day after day[2]

- Ismo patients were able to exercise at least as well on Day 14 as on Day 1

Predictable pharmacokinetics

- Nearly 100% bioavailable
- No first-pass hepatic metabolism
- Consistent blood levels from patient to patient

*Ismo is active for at least 12 hours after the first dose (ie, 5 hours after the second dose) of each day. The dosing recommendation for Ismo is 20 mg, twice daily, 7 hours apart (with a 17-hour dose-free interval) to maintain efficacy and to avoid tolerance.

Ismo is not recommended for use in aborting acute anginal episodes. The most common side effect, headache, may be managed with simple analgesics. As with other long-acting nitrates, Ismo is not recommended in patients with acute myocardial infarction or congestive heart failure.

Please see brief summary of prescribing information on adjacent page.

TAKE EFFECTIVE CONTROL OF BED-WETTING

- Rapid response–substantial effect seen in as little as 1 to 3 nights of therapy[1]
- A combined 15-year record of successful and safe use in the U.S. and Europe[2]
- May be used hand in hand with behavior modification

Nighttime fluid intake should be restricted to decrease the potential occurrence of fluid overload; serum electrolytes should be checked at least once when therapy is continued beyond 7 days.

DDAVP® Nasal Spray

(desmopressin acetate) 5mL

DRY NIGHTS FOR GOOD MORNINGS

Please see brief summary of prescribing information on adjacent page.

DDAVP® Nasal Spray
(desmopressin acetate) 5mL

Dry Nights For Good Mornings

Brief Summary
CONTRAINDICATION: Known hypersensitivity to DDAVP Nasal Spray.
WARNINGS:
1. For intranasal use only.
2. In very young and elderly patients in particular, fluid intake should be adjusted in order to decrease the potential occurrence of water intoxication and hyponatremia. Particular attention should be paid to the possibility of the rare occurrence of an extreme decrease in plasma osmolality and resulting seizures.
PRECAUTIONS:
General: DDAVP Nasal Spray at high dosage has infrequently produced a slight elevation of blood pressure, which disappeared with a reduction in dosage. The drug should be used with caution in patients with coronary artery insufficiency and/or hypertensive cardiovascular disease because of possible rise in blood pressure.
DDAVP Nasal Spray should be used with caution in patients with conditions associated with fluid and electrolyte imbalance, such as cystic fibrosis, because these patients are prone to hyponatremia.
Central Cranial Diabetes Insipidus: Since DDAVP Nasal Spray is used intranasally, changes in the nasal mucosa such as scarring, edema, or other disease may cause erratic, unreliable absorption in which case DDAVP Nasal Spray should not be used. For such situations, DDAVP injection should be considered.
Primary Nocturnal Enuresis: If changes in the nasal mucosa have occurred, unreliable absorption may result. DDAVP Nasal Spray should be discontinued until the nasal problems resolve.
Information for Patients: Patients should be informed that the bottle accurately delivers 50 doses of 10 mcg each. Any solution remaining after 50 doses should be discarded since the amount delivered thereafter may be substantially less than 10 mcg of drug. No attempt should be made to transfer remaining solution to another bottle. Patients should be instructed to read accompanying directions on use of the spray pump carefully before use.
Laboratory Tests: Laboratory tests for following the patient with central cranial diabetes insipidus or post-surgical or head trauma-related polyuria and polydipsia include urine volume and osmolality. In some cases plasma osmolality may be required. For the healthy patient with primary nocturnal enuresis, serum electrolytes should be checked at least once if therapy is continued beyond 7 days.
Drug Interactions: Although the pressor activity of DDAVP Nasal Spray is very low compared to the antidiuretic activity, use of large doses of DDAVP Nasal Spray with other pressor agents should only be done with careful patient monitoring.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Teratology studies in rats have shown no abnormalities. No further information is available.
Pregnancy-Category B: Reproduction studies performed in rats and rabbits with doses up to 12.5 times the human intranasal dose (i.e. about 125 times the total adult human dose given systemically) have revealed no evidence of harm to the fetus due to desmopressin acetate. There are several publications of management of diabetes insipidus in pregnant women with no harm to the fetus reported; however, no controlled studies in pregnant women have been carried out. Published reports stress that, as opposed to preparations containing the natural hormones, DDAVP Nasal Spray (desmopressin acetate) in antidiuretic doses has no uterotonic action, but the physician will have to weigh possible therapeutic advantages against possible dangers in each individual case.
Nursing Mothers: There have been no controlled studies in nursing mothers. A single study in a post-partum woman demonstrated a marked change in plasma, but little if any change in assayable DDAVP Nasal Spray in breast milk following an intranasal dose of 10 mcg.
Pediatric Use: Primary Nocturnal Enuresis: DDAVP Nasal Spray has been used in childhood nocturnal enuresis. Short-term (4-8 weeks) DDAVP Nasal Spray administration has been shown to be safe and modestly effective in children aged 6 years or older with severe childhood nocturnal enuresis. Adequately controlled studies with DDAVP Nasal Spray in primary nocturnal enuresis have not been conducted beyond 4-8 weeks. The dose should be individually adjusted to achieve the best results.
Central Cranial Diabetes Insipidus: DDAVP Nasal Spray has been used in children with diabetes insipidus. Use in infants and children will require careful fluid intake restriction to prevent possible hyponatremia and water intoxication. The dose must be individually adjusted to the patient with attention in the very young to the danger of an extreme decrease in plasma osmolality with resulting convulsions. Dose should start at 0.05 mL or less.
Since the spray cannot deliver less than 0.1 mL (10 mcg), smaller doses should be administered using the rhinal tube delivery system. Do not use the nasal spray in pediatric patients requiring less than 0.1 mL (10 mcg) per dose.
There are reports of an occasional change in response with time, usually greater than 6 months. Some patients may show a decreased responsiveness, others a shortened duration of effect. There is no evidence this effect is due to the development of binding antibodies but may be due to a local inactivation of the peptide.
ADVERSE REACTIONS: Infrequently, high dosages have produced transient headache and nausea. Nasal congestion, rhinitis and flushing have also been reported occasionally along with mild abdominal cramps. These symptoms disappeared with reduction in dosage. Nose-bleed, sore throat, cough and upper respiratory infections have also been reported.
The following table lists the percent of patients having adverse experiences without regard to relationship to study drug from the pooled pivotal study data for nocturnal enuresis.

ADVERSE REACTION	PLACEBO (N=59) %	DDAVP 20 mcg (N=60) %	DDAVP 40 mcg (N=61) %
BODY AS A WHOLE			
Abdominal Pain	0	2	2
Asthenia	0	0	2
Chills	0	0	2
Headache	0	2	5
Throat Pain	2	0	0
NERVOUS SYSTEM			
Depression	2	0	0
Dizziness	0	0	3
RESPIRATORY SYSTEM			
Epistaxis	2	3	0
Nostril Pain	0	2	0
Respiratory Infection	2	0	0
Rhinitis	2	8	3
CARDIOVASCULAR SYSTEM			
Vasodilation	2	0	0
DIGESTIVE SYSTEM			
Gastrointestinal Disorder	0	2	0
Nausea	0	0	2
SKIN & APPENDAGES			
Leg Rash	2	0	0
Rash	2	0	0
SPECIAL SENSES			
Conjunctivitis	0	2	0
Edema Eyes	0	2	0
Lachrymation Disorder	0	0	2

OVERDOSAGE: See adverse reactions above. In case of overdosage, the dose should be reduced, frequency of administration decreased, or the drug withdrawn according to the severity of the condition. There is no known specific antidote for DDAVP Nasal Spray. An oral LD_{50} has not been established. An intravenous dose of 2 mg/kg in mice demonstrated no effect.
HOW SUPPLIED: A 5-mL bottle with spray pump delivering 50 doses of 10 mcg (NDC 0075-2450-02). Also available as 2.5 mL per vial, packaged with two rhinal tube applicators per carton (NDC 0075-2450-01). Keep refrigerated at 2°-8°C (36°-46°F). When traveling, product will maintain stability for up to 3 weeks when stored at room temperature, 22°C (72°F).
CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.
Please see full prescribing information in product circular.

References:
1. **Aladjem M,** Wohl R, Boichis H, et al: Desmopressin in nocturnal enuresis. *Arch Dis Child* 1982;57:137-140.
2. **Bloom DA:** The American experience with desmopressin. *Clin Pediatr* 1993(July, special edition):28-31.

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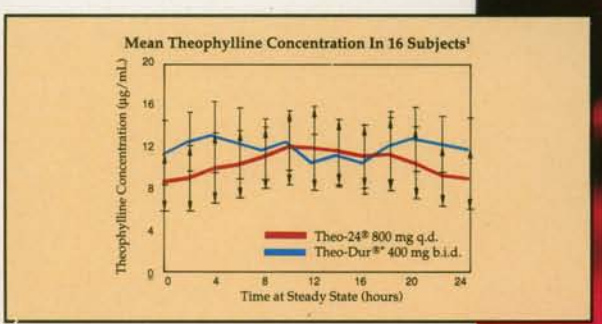
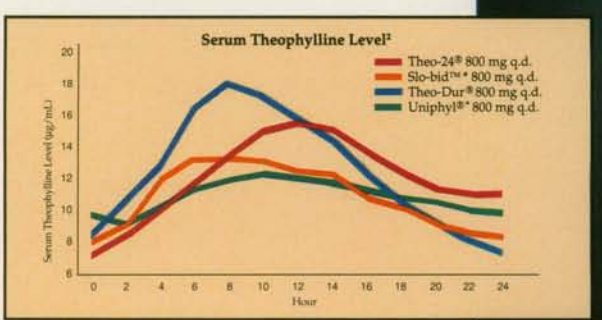
- Now the simpler titration of a complete line: 100, 200, 300 and 400 mg capsules
- Pulmonary function and symptomatic control comparable to b.i.d. theophylline products
- In a crossover study, mean plasma concentrations comparable to those of a b.i.d. product.



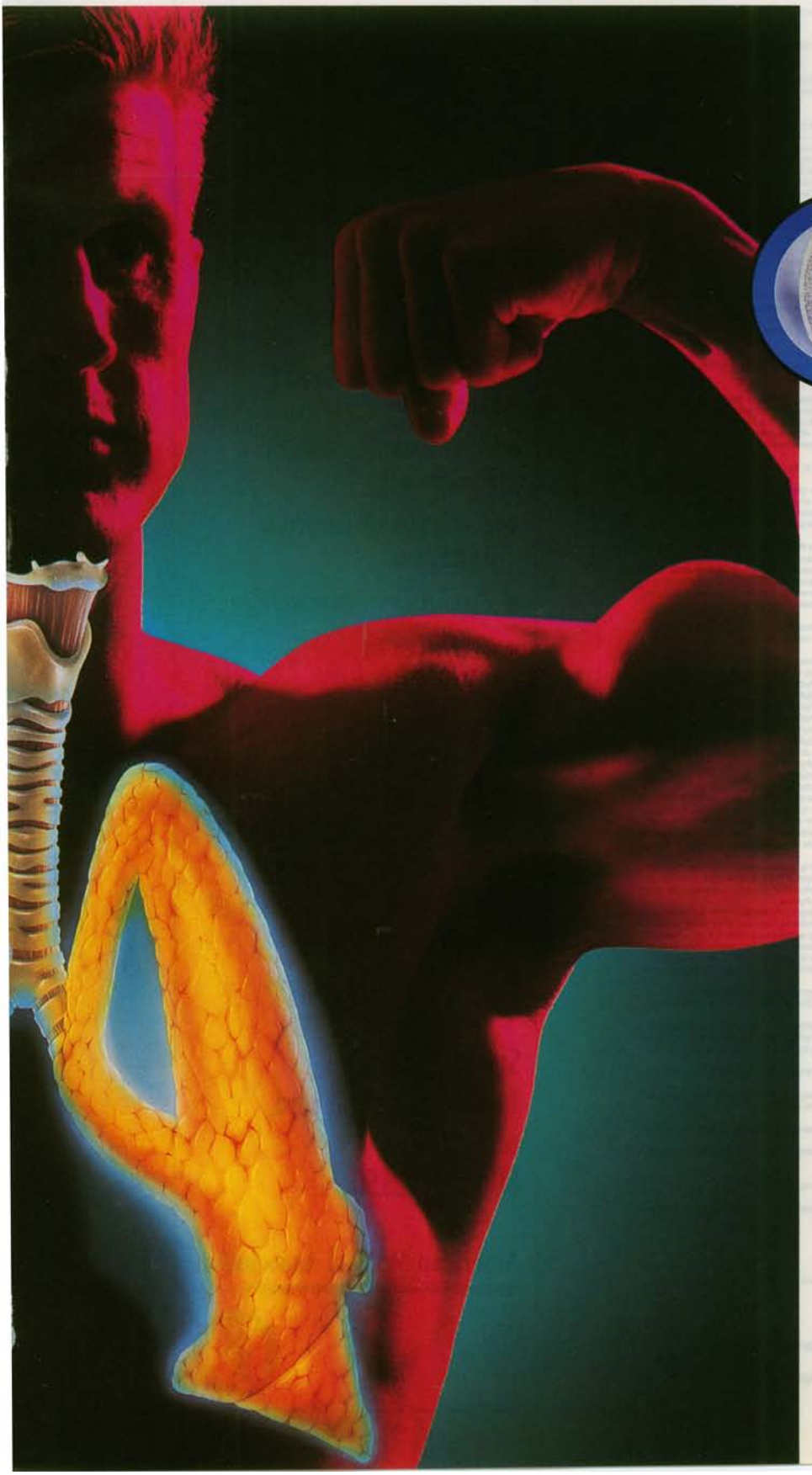
Data on file at Whitby Pharmaceuticals, Inc.[1]

- In a separate study comparing q.d. theophyllines, added evidence of reliable 24-hour delivery

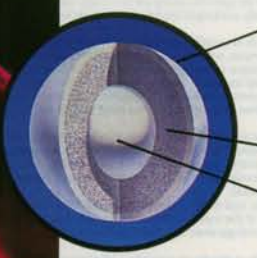


Adapted from Minotti.[2]

ENGTH Theo-24®
(theophylline anhydrous)



- The once-a-day convenience of 24-hour symptom control with unique ProBeads™ delivery



Timing complex allows passage of GI fluids to gradually dissolve theophylline

Anhydrous theophylline

Central core absorbs GI fluids and promotes theophylline release

As with all theophylline products, rapid metabolizers may require higher doses and/or more frequent dosing. For dosage guidelines, including initiation of therapy, titration, and adjustment of dose, please consult complete prescribing information. For patients who require a relatively high dose of theophylline (i.e. 900 mg or 13 mg/kg, whichever is less), please consult Precautions section of the complete prescribing information. Extended-release products are not intended for the treatment of acute attacks of bronchospasm.

*Theo-Dur® is a registered trademark of Key Pharmaceuticals, Inc. Uniphyl® is a registered trademark of The Purdue Frederick Company. Slo-bid™ is a trademark of Rhône-Poulenc Rorer Pharmaceuticals Inc. Please see following page for references and brief summary of prescribing information.

New
400 mg Strength!

Theo-24®
(theophylline anhydrous)

Extended-release capsules 100, 200, 300 & 400 mg

Whitby® Pharmaceuticals

Now 400 mg Strong!

Theo-24®

(theophylline anhydrous)

Extended-release capsules 100, 200, 300 & 400 mg

The following is a brief summary only. Before prescribing, consult complete prescribing information in product labeling or PDR.

INDICATIONS AND USAGE

Theo-24 is indicated for relief and/or prevention of symptoms from asthma and for reversible bronchospasm associated with chronic bronchitis and emphysema.

CONTRAINDICATIONS

Theo-24 is contraindicated in patients with a history of hypersensitivity to theophylline. It is also contraindicated in patients with active peptic ulcer disease and in patients with underlying seizure disorders (unless receiving appropriate anticonvulsant medication).

WARNINGS

Serum levels above 20 mcg/ml are rarely found after appropriate administration of the recommended doses. However, in individuals in whom theophylline plasma clearance is reduced *for any reason*, even conventional doses may result in increased serum levels and potential toxicity. Reduced theophylline clearance has been documented in the following readily identifiable groups: (1) patients with impaired liver function; (2) patients over 55 years of age, particularly males and those with chronic lung disease; (3) patients with cardiac failure from any cause; (4) patients with sustained high fever; (5) infants under 1 year of age; and (6) patients taking certain drugs (see *Precautions: Drug/Drug interactions*). Frequently, such patients have markedly prolonged theophylline serum levels following discontinuation of the drug.

Reduction of dosage and laboratory monitoring is especially appropriate in the above individuals.

Serious side effects such as ventricular arrhythmias, convulsions, or even death may appear as the first sign of toxicity without any previous warning. Less serious signs of theophylline toxicity (ie, nausea and restlessness) may occur frequently when initiating therapy, but are usually transient; when such signs are persistent during maintenance therapy, they are often associated with serum concentrations above 20 mcg/ml. *Serious toxicity is not reliably preceded by less severe side effects.* A serum concentration measurement is the most reliable method of predicting potentially life-threatening toxicity.

Many patients who require theophylline may exhibit tachycardia due to their underlying disease process so that the cause/effect relationship to elevated serum theophylline concentrations may not be recognized.

Theophylline products may cause arrhythmia and/or worsen preexisting arrhythmias. Any significant change in rate and/or rhythm warrants monitoring and further investigation. Halothane anesthesia in the presence of theophylline may produce sinus tachycardia or ventricular arrhythmias.

Studies in laboratory animals (minipigs, rodents, and dogs) recorded the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of necrosis of the myocardium) when theophylline and beta agonists were administered concomitantly. The significance of these findings when applied to humans is unknown.

PRECAUTIONS

General: On the average, theophylline's half-life is shorter in cigarette and marijuana smokers than in nonsmokers, but smokers can have half-lives as long as nonsmokers. Theophylline should not be administered concomitantly with other xanthines. Use with caution in patients with hypoxemia, hypertension, or those with a history of peptic ulcer. Theophylline may occasionally act as a local irritant to the gastrointestinal tract when administered orally, although gastrointestinal symptoms are more commonly centrally mediated and associated with serum drug concentrations over 20 mcg/ml.

Information for patients: Patients should be instructed to take this medication in the morning, at approximately the same time each day, and not to exceed the prescribed dose.

Patients who require a relatively high dose of theophylline (ie, a dose equal to or greater than 900 mg or 13 mg/kg, whichever is less) should be informed of important considerations relating to time of drug administration and meal content (see *Precautions: Drug/Food interactions;* and *Dosage and Administration* in complete prescribing).

As with any extended-release theophylline product the patient should alert the physician if symptoms occur repeatedly, especially near the end of a dosing interval.

Laboratory tests: Serum levels should be monitored periodically to determine the theophylline level associated with observed clinical response and as the method of predicting toxicity. For such measurements, the serum sample should be obtained at the time of peak concentrations, approximately 12 hours after administration of a morning dose. It is important that the patient has not missed or taken additional doses during the previous 72 hours and that dosing intervals have been reasonably consistent. Dose adjustment based on measurements when these instructions have not been followed may result in toxicity (see *Dosage and Administration* in complete prescribing).

Drug Interactions

Drug/Drug interactions: Toxic synergism has been documented with ephedrine and may occur with other sympathomimetic bronchodilators. Halothane anesthesia in the presence of theophylline may produce sinus tachycardia or ventricular arrhythmias.

In addition, the following drug interactions have been demonstrated with theophylline:

Lithium carbonate	Increased renal excretion of lithium
Allopurinol (high-dose)	Increased serum theophylline levels
Cimetidine	Increased serum theophylline levels
Erythromycin, troleandomycin	Increased serum theophylline levels
Oral contraceptive steroids	Increased serum theophylline levels
Ciprofloxacin	Increased serum theophylline levels
Propranolol	Increased serum theophylline levels
Phenytoin	Decreased theophylline and phenytoin serum levels
Carbamazepine	Decreased serum theophylline levels
Phenobarbital	Decreased serum theophylline levels
Rifampin	Decreased serum theophylline levels

Drug/Food interactions: Taking Theo-24 less than one hour before a high-fat-content meal, such as 8 oz whole milk, 2 fried eggs, 2 bacon strips, 2 oz hashed brown potatoes, and 2 slices of buttered toast (about 985 calories, including approximately 71 g of fat) may result in a significant increase in peak serum level and in the extent of absorption of theophylline as compared to administration in the fasted state. In some cases (especially with doses of 900 mg or more taken less than one hour before a high-fat-content meal) serum theophylline levels may exceed the 20 mcg/ml level, above which theophylline toxicity is more likely to occur.

Drug/Laboratory test interactions: Currently available analytical methods, including high pressure liquid chromatography and immunoassay techniques, for measuring serum theophylline levels are specific. Metabolites and other drugs generally do not affect the results. Other new analytical methods are in use. The physician should be aware of the laboratory method used and whether other drugs will interfere with the assay for theophylline.

Carcinogenesis, mutagenesis, and impairment of fertility: Long-term carcinogenicity studies have not been performed with theophylline. Theophylline has been shown to be mutagenic in *Escherichia coli* and other lower organisms *(Euglena gracilis* and *Ophiostoma multiannulatum).* Chromosome-breaking activity was detected in human cell cultures at concentrations of theophylline up to 50 times the therapeutic serum concentration in humans. Theophylline was not mutagenic in the dominant lethal assay in male mice given theophylline intraperitoneally in doses up to 30 times the maximum daily human oral dose. Studies to determine the effect on fertility have not been performed with theophylline.

Pregnancy: Pregnancy Category C. Limited animal studies have shown teratogenic activity of theophylline in mice and rats. There are no adequate and well-controlled studies in pregnant women. Theophylline should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers: Theophylline is distributed into breast milk and may cause irritability or other signs of toxicity in nursing infants. Because of the potential for serious adverse reactions in nursing infants from theophylline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric use: Safety and effectiveness in children under 12 years of age have not been established with this product.

ADVERSE REACTIONS

The following adverse reactions have been observed, but there has not been enough systematic collection of data to support an estimate of their frequency. The most consistent adverse reactions are usually due to overdosage.

Gastrointestinal: nausea, vomiting, epigastric pain, hematemesis, diarrhea.

Central nervous system: headaches, irritability, restlessness, insomnia, reflex hyperexcitability, muscle twitching, clonic and tonic generalized convulsions.

Cardiovascular: palpitation, tachycardia, extrasystoles, flushing, hypotension, circulatory failure, ventricular arrhythmias.

Respiratory: tachypnea.

Renal: potentiation of diuresis.

Other: alopecia, hyperglycemia, inappropriate ADH (antidiuretic hormone) syndrome, rash.

HOW SUPPLIED

Theo-24 (theophylline anhydrous) is supplied in extended-release capsules containing 100, 200, 300 or 400 mg of anhydrous theophylline.

Caution: Federal law prohibits dispensing without prescription.

Revised 8/93

References: 1.Data on file. 2. Minotti DA, Altman LC, Ayars GH et al, Once-a-day dosing with theophylline: a comparison of four sustained-release products. *Ann Allergy 68*: 500-506, 1992.

Whitby® Pharmaceuticals

Manufactured for Whitby Pharmaceuticals, Inc., Richmond, VA 23220, by G. D. Searle & Co., Chicago, IL 60680.

Once-A-Day

Adalat® CC

nifedipine EXTENDED RELEASE TABLETS

30mg, 60mg & 90mg

Real Value for Real People with Hypertension

Real Therapeutic Value

- The benefits of long-acting nifedipine therapy for hypertension*[1]

Real Human Value

- Convenient, well-tolerated therapy
- Peripheral edema and headache were the most common dose-related adverse events reported; flushing/heat sensation, dizziness, and fatigue/asthenia were all reported at an incidence of 4%

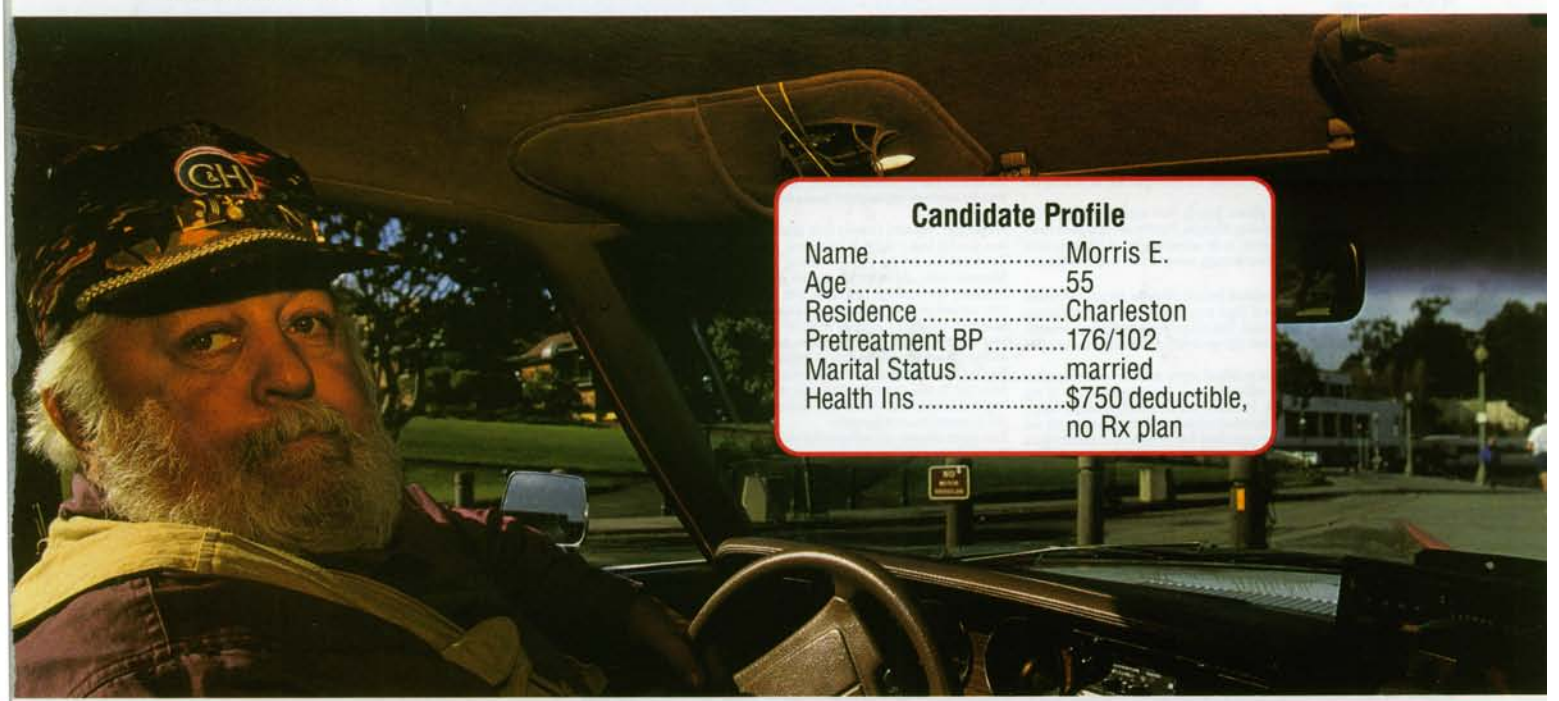
Real Economic Value

- Lower price (AWP) than Procardia XL® 30 mg, 60 mg and 90 mg—**potential 25% savings**†[2]

*Not indicated for angina. Take on an empty stomach. Careful titration may be necessary when switching between Procardia XL® and Adalat® CC. Procardia XL is a registered trademark of Pfizer Labs Division, Pfizer Inc.

†Calculations based on suggested Average Wholesale Price (AWP).

Please see brief summary of Prescribing Information on back of this page.



Candidate Profile

Name	Morris E.
Age	55
Residence	Charleston
Pretreatment BP	176/102
Marital Status	married
Health Ins	$750 deductible, no Rx plan

"Save up to $192† a year? That's the next payment on my insurance."

Once-A-Day

Adalat® CC

nifedipine EXTENDED RELEASE TABLETS

30mg, 60mg & 90mg

Start with*

℞

Adalat CC
30mg
once daily

Titrate, if necessary*

℞

Adalat CC
60mg
once daily

*Please see DOSAGE AND ADMINISTRATION section in brief summary of Prescribing Information below.

BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION
For Oral Use

PZ100744BS 5/93

INDICATION AND USAGE: ADALAT CC is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

CONTRAINDICATIONS: Known hypersensitivity to nifedipine.

WARNINGS: Excessive Hypotension: Although in most patients the hypotensive effect of nifedipine is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients using concomitant beta-blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients who received immediate release capsules together with a beta-blocking agent and who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of nifedipine and a beta-blocker, but the possibility that it may occur with nifedipine alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In nifedipine-treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for nifedipine to be washed out of the body prior to surgery.

Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those who have severe obstructive coronary artery disease, have developed well documented increased frequency, duration and/or severity of angina or acute myocardial infarction upon starting nifedipine or at the time of dosage increase. The mechanism of this effect is not established.

Beta-Blocker Withdrawal: When discontinuing a beta-blocker it is important to taper its dose, if possible, rather than stopping abruptly before beginning nifedipine. Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of nifedipine treatment will not prevent this occurrence and on occasion has been reported to increase it.

Congestive Heart Failure: Rarely, patients (usually while receiving a beta-blocker) have developed heart failure after beginning nifedipine. Patients with tight aortic stenosis may be at greater risk for such an event, as the unloading effect of nifedipine would be expected to be of less benefit to these patients, owing to their fixed impedance to flow across the aortic valve.

PRECAUTIONS: General - Hypotension: Because nifedipine decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of ADALAT CC is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure (See WARNINGS).

Peripheral Edema: Mild to moderate peripheral edema occurs in a dose-dependent manner with ADALAT CC. The placebo subtracted rate is approximately 8% at 30 mg, 12% at 60 mg and 19% at 90 mg daily. This edema is a localized phenomenon, thought to be associated with vasodilation of dependent arterioles and small blood vessels and not due to left ventricular dysfunction or generalized fluid retention. With patients whose hypertension is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Information for Patients: ADALAT CC is an extended release tablet and should be swallowed whole and taken on an empty stomach. It should not be administered with food. Do not chew, divide or crush tablets.

Laboratory Tests: Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted. The relationship to nifedipine therapy is uncertain in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symptoms; however, cholestasis with or without jaundice has been reported. A small increase (<5%) in mean alkaline phosphatase was noted in patients treated with ADALAT CC. This was an isolated finding and it rarely resulted in values which fell outside the normal range. Rare instances of allergic hepatitis have been reported with nifedipine treatment. In controlled studies, ADALAT CC did not adversely affect serum uric acid, glucose, cholesterol or potassium.

Nifedipine, like other calcium channel blockers, decreases platelet aggregation *in vitro*. Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time in some nifedipine patients. This is thought to be a function of inhibition of calcium transport across the platelet membrane. No clinical significance for these findings has been demonstrated.

Positive direct Coombs' test with or without hemolytic anemia has been reported but a causal relationship between nifedipine administration and positivity of this laboratory test, including hemolysis, could not be determined.

Although nifedipine has been used safely in patients with renal dysfunction and has been reported to exert a beneficial effect in certain cases, rare reversible elevations in BUN and serum creatinine have been reported in patients with pre-existing chronic renal insufficiency. The relationship to nifedipine therapy is uncertain in most cases but probable in some.

Drug Interactions: Beta-adrenergic blocking agents: (See WARNINGS).

ADALAT CC was well tolerated when administered in combination with a beta blocker in 187 hypertensive patients in a placebo-controlled clinical trial. However, there have been occasional literature reports suggesting that the combination of nifedipine and beta-adrenergic blocking drugs may increase the likelihood of congestive heart failure, severe hypotension, or exacerbation of angina in patients with cardiovascular disease.

Digitalis: Since there have been isolated reports of patients with elevated digoxin levels, and there is a possible interaction between digoxin and ADALAT CC, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing ADALAT CC to avoid possible over- or under-digitalization.

Coumarin Anticoagulants: There have been rare reports of increased prothrombin time in patients taking coumarin anticoagulants to whom nifedipine was administered. However, the relationship to nifedipine therapy is uncertain.

Quinidine: There have been rare reports of an interaction between quinidine and nifedipine (with a decreased plasma level of quinidine).

Cimetidine: Both the peak plasma level of nifedipine and the AUC may increase in the presence of cimetidine. Ranitidine produces smaller non-significant increases. This effect of cimetidine may be mediated by its known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of nifedipine. If nifedipine therapy is initiated in a patient currently receiving cimetidine, cautious titration is advised.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Nifedipine was administered orally to rats for two years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose. *In vivo* mutagenicity studies were negative.

Pregnancy: Pregnancy Category C. In rodents, rabbits and monkeys, nifedipine has been shown to have a variety of embryotoxic, placentotoxic and fetotoxic effects, including stunted fetuses (rats, mice and rabbits), digital anomalies (rats and rabbits), rib deformities (mice), cleft palate (mice), small placentas and underdeveloped chorionic villi (monkeys), embryonic and fetal deaths (rats, mice and rabbits), prolonged pregnancy (rats; not evaluated in other species), and decreased neonatal survival (rats; not evaluated in other species). On a mg/kg or mg/m^2 basis, some of the doses associated with these various effects are higher than the maximum recommended human dose and some are lower, but all are within an order of magnitude of it.

The digital anomalies seen in nifedipine-exposed rabbit pups are strikingly similar to those seen in pups exposed to phenytoin, and these are in turn similar to the phalangeal deformities that are the most common malformation seen in human children with *in utero* exposure to phenytoin.

There are no adequate and well-controlled studies in pregnant women. ADALAT CC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Nifedipine is excreted in human milk. Therefore, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE EXPERIENCES: The incidence of adverse events during treatment with ADALAT CC in doses up to 90 mg daily were derived from multi-center placebo-controlled clinical trials in 370 hypertensive patients. Atenolol 50 mg once daily was used concomitantly in 187 of the 370 patients on ADALAT CC and in 64 of the 126 patients on placebo. All adverse events reported during ADALAT CC therapy were tabulated independently of their causal relationship to medication.

The most common adverse event reported with ADALAT® CC was peripheral edema. This was dose related and the frequency was 18% on ADALAT CC 30 mg daily, 22% on ADALAT CC 60 mg daily and 29% on ADALAT CC 90 mg daily versus 10% on placebo.

Other common adverse events reported in the above placebo-controlled trials include: Headache (19%, versus 13% placebo incidence); Flushing/heat sensation (4%, versus 0% placebo incidence); Dizziness (4%, versus 2% placebo incidence); Fatigue/asthenia (4%, versus 4% placebo incidence); Nausea (2%, versus 1% placebo incidence); Constipation (1%, versus 0% placebo incidence).

Where the frequency of adverse events with ADALAT CC and placebo is similar, causal relationship cannot be established.

The following adverse events were reported with an incidence of 3% or less in daily doses up to 90 mg:

Body as a Whole/Systemic: chest pain, leg pain **Central Nervous System:** paresthesia, vertigo **Dermatologic:** rash **Gastrointestinal:** constipation **Musculoskeletal:** leg cramps **Respiratory:** epistaxis, rhinitis **Urogenital:** impotence, urinary frequency

Other adverse events reported with an incidence of less than 1.0% were:

Body as a Whole/Systemic: cellulitis, chills, facial edema, neck pain, pelvic pain, pain **Cardiovascular:** atrial fibrillation, bradycardia, cardiac arrest, extrasystole, hypotension, palpitations, phlebitis, postural hypotension, tachycardia, cutaneous angiectases **Central Nervous System:** anxiety, confusion, decreased libido, depression, hypertonia, insomnia, somnolence **Dermatologic:** pruritus, sweating **Gastrointestinal:** abdominal pain, diarrhea, dry mouth, dyspepsia, esophagitis, flatulence, gastrointestinal hemorrhage, vomiting **Hematologic:** lymphadenopathy **Metabolic:** gout, weight loss **Musculoskeletal:** arthralgia, arthritis, myalgia **Respiratory:** dyspnea, increased cough, rales, pharyngitis **Special Senses:** abnormal vision, amblyopia, conjunctivitis, diplopia, tinnitus **Urogenital/Reproductive:** kidney calculus, nocturia, breast engorgement

The following adverse events have been reported rarely in patients given nifedipine in other formulations: allergenic hepatitis, alopecia, anemia, arthritis with ANA (+), depression, erythromelalgia, exfoliative dermatitis, fever, gingival hyperplasia, gynecomastia, leukopenia, mood changes, muscle cramps, nervousness, paranoid syndrome, purpura, shakiness, sleep disturbances, syncope, taste perversion, thrombocytopenia, transient blindness at the peak plasma level, tremor and urticaria.

DOSAGE AND ADMINISTRATION: Dosage should be adjusted according to each patient's needs. It is recommended that ADALAT CC be administered orally once daily on an empty stomach. ADALAT CC is an extended release dosage form and tablets should be swallowed whole, not bitten or divided. In general, titration should proceed over a 7-14 day period starting with 30 mg once daily. Upward titration should be based on therapeutic efficacy and safety. The usual maintenance dose is 30 mg to 60 mg once daily. Titration to doses above 90 mg daily is not recommended.

If discontinuation of ADALAT CC is necessary, sound clinical practice suggests that the dosage should be decreased gradually with close physician supervision.

Care should be taken when dispensing ADALAT CC to assure that the extended release dosage form has been prescribed.

PZ100744BS 5/93 3060
Printed in USA

Real People, Real Needs, Real Value

References:
1. Data on file, Miles Inc.
2. *Redbook Update.* Montvale, NJ, Medical Economics Data, Inc., October 1993;p. 34.

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Pharmaceutical Division

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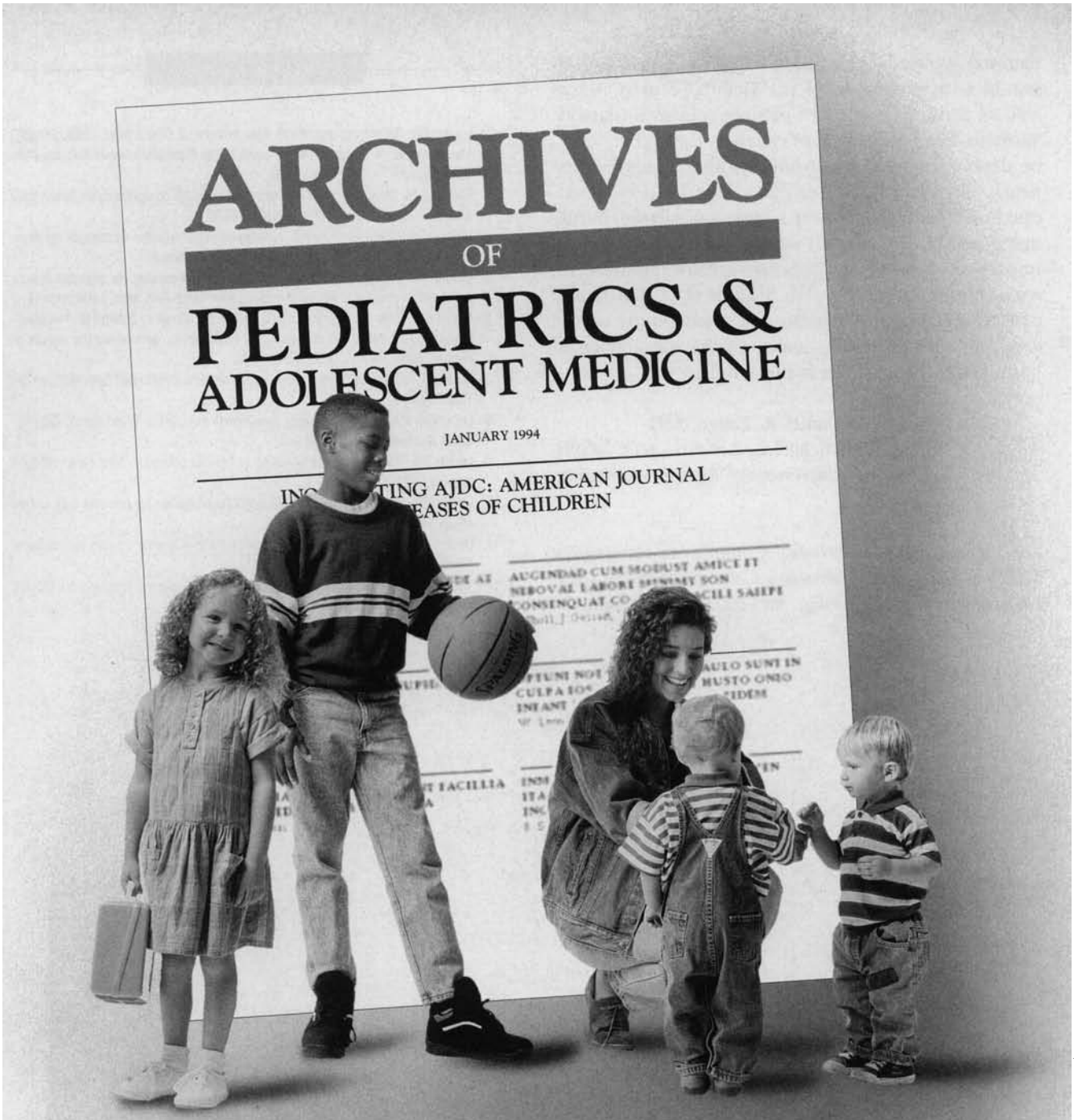

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NOW FOR ANGINA

THE ONE

CARDIZEM® CD

(diltiazem HCl) 120-, 180-, 240-, 300-mg Capsules

PROVEN 24-HOUR CONTROL OF BOTH ANGINA AND HYPERTENSION[1,2]

Please see brief summary of prescribing information on adjacent page.

0115A3

ONCE-A-DAY CARDIZEM® CD

(diltiazem HCl)

24-HOUR CONTROL OF BOTH ANGINA AND HYPERTENSION

Brief Summary of
Prescribing Information as of October 1992 (2)

CARDIZEM® CD (diltiazem HCl)

Capsules

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

1. **Cardiac Conduction**. CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (13 of 3,290 patients or 0.40%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure**. Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ±6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of CARDIZEM (diltiazem hydrochloride) in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.
3. **Hypotension**. Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury**. Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General

CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters of renal and hepatic function should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interactions

Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.) Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs such as cyclosporin, particularly those of low therapeutic ratig or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers. Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. In vitro, propranolol appears to be displaced from its binding sites by diltiazem. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine. A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1200 mg per day and a single dose of diltiazem 60 mg. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis. Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics. The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Available as Once-A-Day


120-mg capsules


180-mg capsules


240-mg capsules


300-mg capsules

℞ Cardizem CD
Start with one
180-mg
capsule daily

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy

Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The following table presents the most common adverse reactions reported in placebo-controlled angina and hypertension trials in patients receiving CARDIZEM CD up to 360 mg with rates in placebo patients shown for comparison.

CARDIZEM CD Capsule Placebo-Controlled Angina and Hypertension Trials Combined

Adverse Reaction	CARDIZEM CD N=607	Placebo N=301
Headache	5.4%	5.0%
Dizziness	3.0%	3.0%
Bradycardia	3.3%	1.3%
AV Block First Degree	3.3%	0.0%
Edema	2.6%	1.3%
ECG Abnormality	1.6%	2.3%
Asthenia	1.8%	1.7%

In clinical trials of CARDIZEM CD Capsules, CARDIZEM Tablets, and CARDIZEM SR Capsules involving over 3200 patients, the most common events (ie, greater than 1%) were edema (4.6%), headache (4.6%), dizziness (3.5%), asthenia (2.6%), first-degree AV block (2.4%), bradycardia (1.7%), flushing (1.4%), nausea (1.4%), and rash (1.2%).

In addition, the following events were reported infrequently (less than 1%) in angina or hypertension trials:

Cardiovascular: Angina, arrhythmia, AV block (second- or third-degree), bundle branch block, congestive heart failure, ECG abnormalities, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles

Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor

Gastrointestinal: Anorexia, constipation, diarrhea, dry mouth, dysgeusia, dyspepsia, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see hepatic warnings), thirst, vomiting, weight increase

Dermatological: Petechiae, photosensitivity, pruritus, urticaria

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, erythema multiforme, exfoliative dermatitis, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A number of well-documented cases of generalized rash, characterized as leukocytoclastic vasculitis, have been reported.

However, a definitive cause and effect relationship between these events and CARDIZEM therapy is yet to be established.

Prescribing Information as of October 1992 (2)

Marion Merrell Dow Inc.
Kansas City, MO 64114

ccdb1092(2)a

References: 1. Data on file, Marion Merrell Dow Inc. **2.** Massie BM, Der E, Herman TS, Topolski P, Park GD, Stewart WH. *Clin Cardiol.* 1992;15:365-368.

MARION MERRELL DOW INC.
PRESCRIPTION PRODUCTS DIVISION
KANSAS CITY, MO 64114

Call for Papers

1994 International Conference on Physician Health
September 16-20, 1994. Ottawa, Ontario, Canada

"Stress: The Profession, the Family and You"

The 1994 International Conference on Physician Health, co-sponsored by the American Medical Association, the Federation of State Medical Boards, the Canadian Medical Association, and the Federation of Medical Licensing Authorities of Canada is scheduled for September 16-20, 1994, at the Ottawa Westin Hotel.

Ottawa is Canada's capital and offers many national museums, over 60 miles of bicycle paths, hiking in Gateneau park, squash courts and swimming at the hotel and golf nearby.

The conference will provide a forum for practitioners and researchers to present recent findings and innovative treatment and education programs in physician health. This conference will address a range of issues, such as AIDS, HIV, problems related to aging, mental illness, substance abuse and physical disabilities and limitations, including those caused by general medical conditions. Possible topics for presentation include: presentation and treatment of health problems among physicians, the impact of disorders on physicians' families and practices, medical-legal issues facing hospital administrations and licensing boards, and material on health promotion and disease prevention. *Abstracts which address issues related to these topics (i.e., prevention, diagnosis, treatment, rehabilitation), but not dealing specifically with physicians are also welcome.*

Three types of presentations regarding these physician health issues are invited:

- **Poster Presentations**
  Written presentations of data-based research, epidemiological research, or program descriptions.

- **Paper Sessions**
  Oral presentation of scientific, data-based findings relative to the topic of physician health.

  Abstracts for poster presentations and paper sessions should contain an introductory statement on the significance of subject matter. Description of methods, results, and conclusions should follow the introductory statement.

- **Workshops**
  Training or instructional presentations, designed to improve specific skills of persons who work in the area of physician health.

  Abstracts for workshops should contain information on the program's intended audience, goals, teaching strategies, and materials. Evaluation data should be summarized

Abstracts may not exceed 200 words. Any abstracts exceeding that length will be rejected. Abstracts should be typed, double spaced, and mailed (not faxed). Four copies of the abstract should be sent, along with one self-addressed, stamped envelope. All submissions must list the primary and secondary authors and their professional affiliations. Telephone number and address of primary author must also be included.

Submissions *must* be received by February 1, 1994.

Abstracts will be submitted for blind review. Abstracts will be judged on their applicability to the conference topic area and their scientific merit. The decisions of the blind reviewers will be communicated to the abstract's primary author by April 1, 1994.

All presenters are expected to register for the conference at the AMA member rate. We are unable to provide any financial support for presenters. Presenters will also be responsible for their own transportation and hotel expenses, as well as making all reservations for same.

Send all materials to:
Elaine M. Tejcek, Physicians Health Foundation, American Medical Association, 515 N. State Street, Chicago, IL 60610.

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FREEDOM FROM COUGH!

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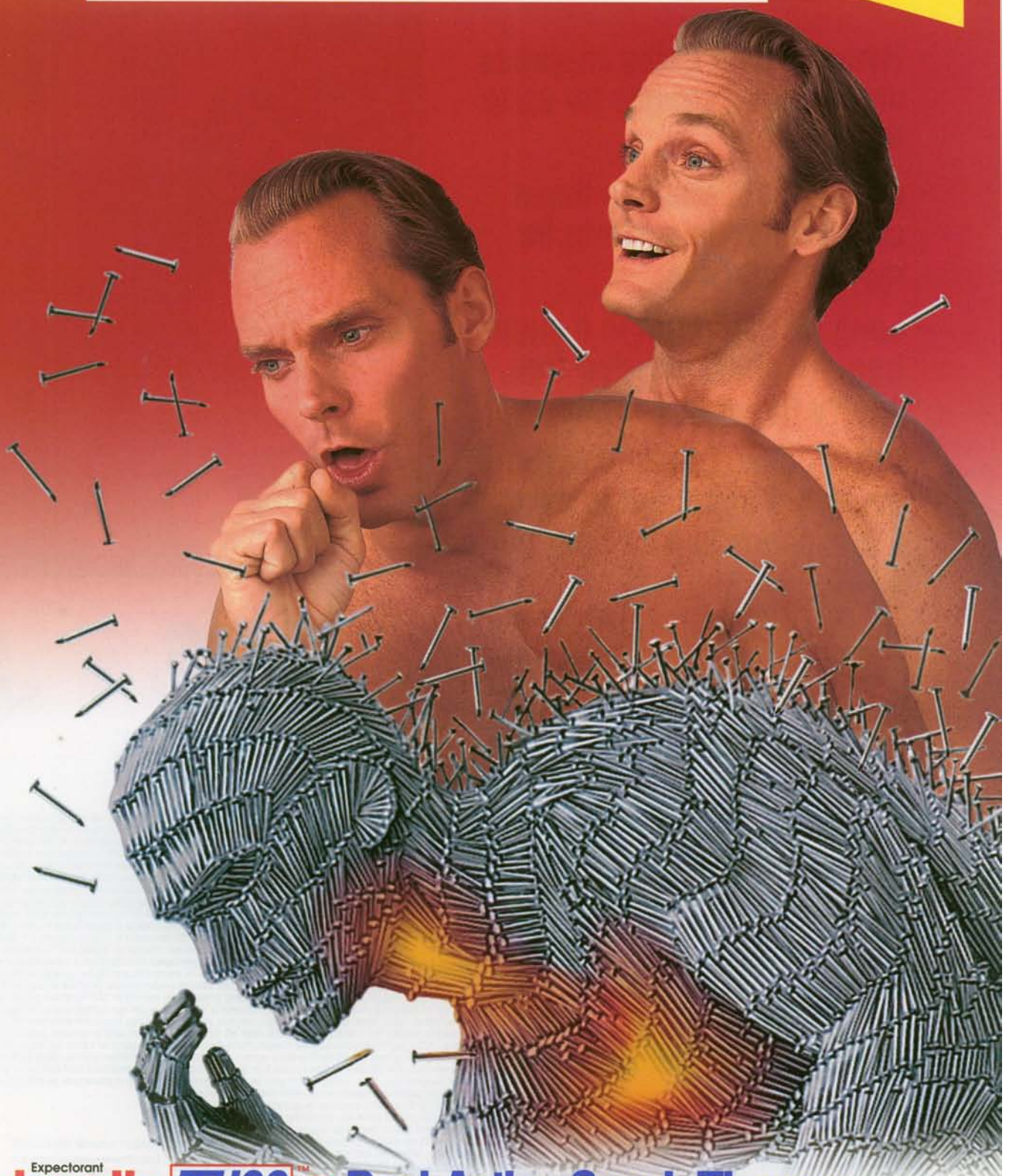
New Expectorant vicodin TUSS™ C III

(hydrocodone bitartrate 5mg (May be habit forming) and guaifenesin 100mg per (5mL) teaspoon)

Sugar Free



Expectorant vicodin TUSS™ C III Dual Action Cough Therapy

New Expectorant

vicodin TUSS™ III

(hydrocodone bitartrate 5mg (Warning: May be habit forming) and guaifenesin 100mg per (5mL) teaspoon)

Combines the antitussive action of hydrocodone with the expectorant action of guaifenesin.

- Hydrocodone helps suppress dry, hacking coughs for up to 6 hours.
- Guaifenesin enables those coughs that do occur to be more productive.
- Long lasting relief in a sugar-free, alcohol-free, dye-free, cherry flavored formula.
- Adult Dose: 1 teaspoon (5mL) every 4-6 hours not to exceed 6 teaspoons in a 24 hour period.

Alcohol Free

New Expectorant

vicodin TUSS™ III

(hydrocodone bitartrate 5mg (Warning: May be habit forming) and guaifenesin 100mg per (5mL) teaspoon)

Sugar Free

Effective cough relief you can phone in.

INDICATIONS AND USAGE: VICODIN TUSS™ Expectorant is indicated for the symptomatic relief of irritating non-productive cough associated with upper and lower respiratory tract congestion. **CONTRAINDICATIONS:** VICODIN TUSS™ Expectorant is contraindicated in patients hypersensitive to hydrocodone or guaifenesin. Patients known to be hypersensitive to other opioids may exhibit cross sensitivity to VICODIN TUSS™ Expectorant. Hydrocodone is contraindicated in the presence of an intracranial lesion associated with increased intracranial pressure; and whenever ventilatory function is depressed. **WARNINGS:** May be habit forming. Hydrocodone can produce drug dependence of the morphine type and therefore has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of VICODIN TUSS™ Expectorant and it should be prescribed and administered with the same degree of caution appropriate to the use of other narcotic drugs (see DRUG ABUSE AND DEPENDENCE). **Respiratory Depression:** VICODIN TUSS™ Expectorant produces dose-related respiratory depression by directly acting on the brain stem respiratory centers. If respiratory depression occurs, it may be antagonized by the use of naloxone hydrochloride and other supportive measures when indicated. **Head Injury and Increased Intracranial Pressure:** The respiratory depressant properties of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries. **Acute Abdominal Conditions:** The administration of VICODIN TUSS™ Expectorant or other opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions. **PRECAUTIONS:** Before prescribing medication to suppress or modify cough, it is important to ascertain that the underlying cause of cough is identified, that modification of cough does not increase the risk of clinical or physiologic complications, and that appropriate therapy for the primary disease is provided. **Usage in Ambulatory Patients:** Hydrocodone, like all narcotics, may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, and patients should be warned accordingly. **Drug Interactions:** Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative hypnotics or other CNS depressants (including alcohol) concomitantly with hydrocodone may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced (see WARNINGS). **Laboratory Interactions:** The metabolite of guaifenesin has been found to produce an apparent increase in urinary 5-hydroxyindoleacetic acid, and guaifenesin therefore may interfere with the interpretation of this test for the diagnosis of carcinoid syndrome. Guaifenesin administration should be discontinued 24 hours prior to the collection of urine specimens for the determination of 5-hydroxyindoleacetic acid. **Carcinogenesis, mutagenesis, impairment of fertility:** Carcinogenicity, mutagenicity and reproduction studies have not been conducted with VICODIN TUSS™ Expectorant. **Usage in Pregnancy:** Pregnancy Category C. Animal reproduction studies have not been conducted with VICODIN TUSS™ Expectorant. It is also not known whether VICODIN TUSS™ Expectorant can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. VICODIN TUSS™ Expectorant should be given to a pregnant woman only if clearly needed. **Nonteratogenic effects:** Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal. Chlorpromazine 0.7-1.0 mg/kg q 6 h, phenobarbital 2 mg/kg q 6 h, and paregoric 2-4 drops/kg q 4 h, have been used to treat withdrawal symptoms in infants. The duration of therapy is 4 to 28 days, with the dosages decreased as tolerated. **Nursing mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from VICODIN TUSS™ Expectorant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. **ADVERSE REACTIONS Respiratory System:** Hydrocodone produces dose-related respiratory depression by acting directly on brain stem respiratory centers. **Cardiovascular System:** Hypertension, postural hypotension and palpitations. **Genitourinary System:** Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported with opiates. **Central Nervous System:** Sedation, drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, dizziness, psychic dependence, mood changes and blurred vision. **Gastrointestinal System:** Nausea and vomiting occur more frequently in ambulatory than in recumbent patients. **DRUG ABUSE AND DEPENDENCE:** Special care should be exercised in prescribing hydrocodone for emotionally unstable patients and for those with a history of drug misuse. Such patients should be closely supervised when long-term therapy is contemplated. VICODIN TUSS™ Expectorant is a Schedule III narcotic. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of narcotics; therefore, VICODIN TUSS™ Expectorant should always be prescribed and administered with caution. Physical dependence is the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome. Patients physically dependent on opioids will develop an abstinence syndrome upon abrupt discontinuation of the opioid or following the administration of a narcotic antagonist. The character and severity of the withdrawal symptoms are related to the degree of physical dependence. Manifestations of opioid withdrawal are similar to but milder than that of morphine and include lacrimation, rhinorrhea, yawning, sweating, restlessness, dilated pupils, anorexia, goose-flesh, irritability, and tremor. In more severe forms, nausea, vomiting, intestinal spasm and diarrhea, increased heart rate and blood pressure, chills, and pains in bones and muscles of the back and extremities may occur. Peak effects will usually be apparent at 48 to 72 hours. Treatment of withdrawal is usually managed by providing sufficient quantities of an opioid to suppress **severe** withdrawal symptoms and then gradually reducing the dose of opioid over a period of several days. **OVERDOSAGE: Signs and Symptoms:** Serious overdosage with VICODIN TUSS™ Expectorant is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage apnea, circulatory collapse, cardiac arrest, and death may occur. **Treatment:** Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonist naloxone hydrochloride is a specific antidote for respiratory depression which may result from overdosage or unusual sensitivity to narcotics including hydrocodone. Therefore, an appropriate dose of naloxone hydrochloride should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. For further information, see full prescribing information for naloxone hydrochloride. An antagonist should not be administered in the absence of clinically significant respiratory depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated. Gastric emptying may be useful in removing unabsorbed drug. Activated charcoal may be of benefit.

QUALITY TOWARD EXCELLENCE
Knoll Pharmaceutical Company
30 North Jefferson Road
Whippany, New Jersey 07981

knoll

BASF Group

V3110/7-93

Printed In U.S.A.

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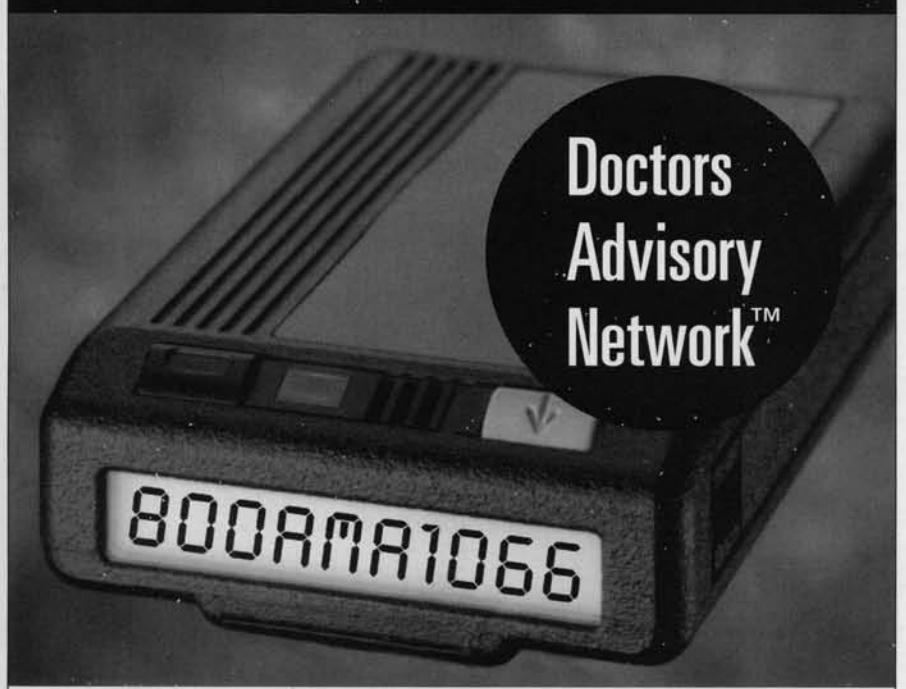

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NAPROSYN®

(NAPROXEN) 500 mg tablets

Brief Summary:

Contraindications: Patients who have had allergic reactions to NAPROSYN, ANAPROX or ANAPROX DS or in whom aspirin or other NSAIDs induce the syndrome of asthma, rhinitis, and nasal polyps. Because anaphylactic reactions usually occur in patients with a history of such reactions, question patients for asthma, nasal polyps, urticaria, and hypotension associated with NSAIDs before starting therapy. If such symptoms occur, discontinue the drug. **Warnings:** Serious GI toxicity such as bleeding, ulceration, and perforation can occur at any time, with or without warning symptoms, in patients treated chronically with NSAIDs. Remain alert for ulceration and bleeding in such patients even in the absence of previous GI tract symptoms. In clinical trials, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur. Studies have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than others and most spontaneous reports of fatal GI events are in this population. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity. **Precautions:** DO NOT GIVE **NAPROSYN®** (NAPROXEN) CONCOMITANTLY WITH **ANAPROX®** (NAPROXEN SODIUM) OR **ANAPROX® DS** (NAPROXEN SODIUM) SINCE THEY BOTH CIRCULATE IN PLASMA AS THE NAPROXEN ANION. Acute interstitial nephritis with hematuria, proteinuria, and nephrotic syndrome has been reported. Patients with impaired renal function, heart failure, liver dysfunction, patients taking diuretics, and the elderly are at greater risk of overt renal decompensation. If this occurs, discontinue the drug. Use with caution and monitor serum creatinine and/or creatinine clearance in patients with significantly impaired renal function. Use caution in patients with baseline creatinine clearance less than 20 mL/minute. Use the lowest effective dose in the elderly or in patients with chronic alcoholic liver disease or cirrhosis. With NSAIDs, borderline elevations of liver tests may occur in up to 15% of patients. They may progress, remain unchanged, or be transient with continued therapy. Elevations of SGPT or SGOT occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and fatal hepatitis, have been reported rarely. If liver disease develops or if systemic manifestations occur (e.g., eosinophilia or rash), discontinue therapy. If steroid dosage is reduced or eliminated during therapy, do so slowly and observe patients closely for adverse effects, including adrenal insufficiency and exacerbation of arthritis symptoms. Determine hemoglobin values periodically for patients with initial values of 10 grams or less who receive long-term therapy. Peripheral edema has been reported. Therefore, use with caution in patients with fluid retention, hypertension or heart failure. The drug's antipyretic and anti-inflammatory activities may reduce fever and inflammation, diminishing their diagnostic value. Conduct ophthalmic studies if any change or disturbance in vision occurs. For patients with restricted sodium intake, note that the suspension contains 8 mg/mL of sodium. **Information for Patients:** Side effects of NSAIDs can cause discomfort and, rarely, there are more serious side effects, such as GI bleeding, which may result in hospitalization and even fatal outcomes. Physicians may wish to discuss with patients the potential risks and likely benefits of NSAID treatment, particularly when they are used for less serious conditions where treatment without NSAIDs may be an acceptable alternative. Patients should use caution for activities requiring alertness if they experience drowsiness, dizziness, vertigo or depression during therapy. **Laboratory Tests:** Because serious GI tract ulceration and bleeding can occur without warning symptoms, follow chronically treated patients for signs and symptoms of these and inform them of the importance of this follow-up. **Drug Interactions:** Use caution when giving concomitantly with coumarin-type anticoagulants; a hydantoin, sulfonamide or sulfonylurea; furosemide; lithium; beta-blockers; probenecid; or methotrexate. **Drug/Laboratory Test Interactions:** The drug may decrease platelet aggregation and prolong bleeding time or increase urinary values for 17-ketogenic steroids. Temporarily stop therapy for 72 hours before doing adrenal function tests. The drug may interfere with urinary assays of 5HIAA. **Carcinogenesis:** A 2-year rat study showed no evidence of carcinogenicity. **Pregnancy:** Category B. Do not use during pregnancy unless clearly needed. Avoid use during late pregnancy. **Nursing Mothers:** Avoid use in nursing mothers. **Pediatric Use:** Single doses of 2.5-5 mg/kg, with total daily dose not exceeding 15 mg/kg/day, are safe in children over 2 years of age. **Adverse Reactions:** In a study, GI reactions were more frequent and severe in rheumatoid arthritis patients on 1,500 mg/day than in those on 750 mg/day. In studies in children with juvenile arthritis, rash and prolonged bleeding times were more frequent, GI and CNS reactions about the same, and other reactions less frequent than in adults. Incidence Greater Than 1%; Probable Causal Relationship: GI: The most frequent complaints related to the GI tract: constipation,* heartburn,* abdominal pain,* nausea,* dyspepsia, diarrhea, stomatitis. CNS: headache,* dizziness,* drowsiness,* light-headedness, vertigo. Dermatologic: itching (pruritus),* skin eruptions,* ecchymoses,* sweating, purpura. Special Senses: tinnitus,* hearing disturbances, visual disturbances. Cardiovascular: edema,* dyspnea,* palpitations. General: thirst. Incidence Less Than 1%; Probable Causal Relationship: GI: abnormal liver function tests, colitis, GI bleeding and/or perforation, hematemesis, jaundice, melena, peptic ulceration with bleeding and/or perforation, vomiting. Renal: glomerular nephritis, hematuria, hyperkalemia, interstitial nephritis, nephrotic syndrome, renal disease, renal failure, renal papillary necrosis. Hematologic: agranulocytosis, eosinophilia, granulocytopenia, leukopenia, thrombocytopenia. CNS: depression, dream abnormalities, inability to concentrate, insomnia, malaise, myalgia and muscle weakness. Dermatologic: alopecia, photosensitive dermatitis, skin rashes. Special Senses: hearing impairment. Cardiovascular: congestive heart failure. Respiratory: eosinophilic pneumonitis. General: anaphylactoid reactions, menstrual disorders, pyrexia (chills and fever). Causal Relationship Unknown: Hematologic: aplastic anemia, hemolytic anemia. CNS: aseptic meningitis, cognitive dysfunction. Dermatologic: epidermal necrolysis, erythema multiforme, photosensitivity reactions resembling porphyria cutanea tarda and epidermolysis bullosa, Stevens-Johnson syndrome, urticaria. GI: non-peptic GI ulceration, ulcerative stomatitis. Cardiovascular: vasculitis. General: angioneurotic edema, hyperglycemia, hypoglycemia. **Overdosage:** May have drowsiness, heartburn, indigestion, nausea, vomiting. A few patients have had seizures. Empty stomach and use usual supportive measures. In animals 0.5 g/kg of activated charcoal reduced plasma levels of naproxen. **Caution:** Federal law prohibits dispensing without prescription. See package insert for full Prescribing Information.

*Incidence of reported reaction 3%-9%. Where unmarked, incidence less than 3%.

SYNTEX

U.S. patent nos. 3,904,682, 3,998,966 and others.

 Rev. 39 September 1990

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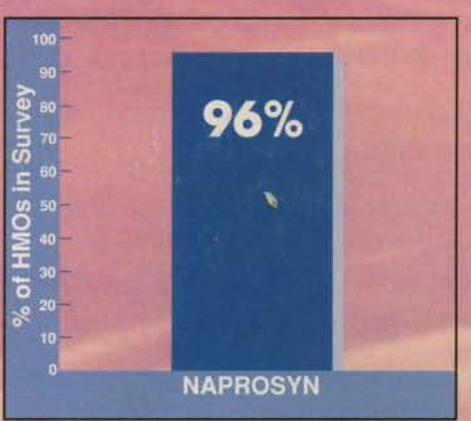

HMO FORMULARY ACCEPTANCE

Please see brief summary of full prescribing information on adjacent page.

*HMO Formulary Drug Audit, first half 1993. Scott Levin Associates, a subsidiary of PMSI. Data on file, Syntex Laboratories, Inc. Document NP94020-H.

SYNTEX

Contraindicated in patients hypersensitive to naproxen, aspirin, or other NSAIDs. As with other NSAIDs, the most frequent adverse events are gastrointestinal. With chronic NSAID therapy, serious G.I. toxicity such as bleeding, ulceration, and perforation can occur. Rare hepatic and renal reactions have been reported.

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EXPECT SUCCESS FROM

NAPROSYN®

(NAPROXEN) 500 mg tablets

Also available in 375 and 250 mg tablets and in suspension 125 mg/5 mL